Division of

CANCER BIOLOGY & DIAGNOSIS

1985 Annual Report Volume II
October 1, 1984-September 30, 1985

U.S. DEPARTMENT
OF HEALTH
AND HUMAN SERVICES

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EXTRAMURAL RESEARCH PROGRAM ANALYSIS

Analysis of the DCBD Extramural Research Program includes both grants and contracts. The use of the research contract has been completely eliminated except for one contract in the Cancer Diagnosis Program which is a long-term study to evaluate the use of the hemoccult test as a screen for the presence of colon cancer. The current extramural contract portfolio of the Division is small and is focused mostly on biological resources important to both basic and clinical cancer research. The major emphasis of the Division favors investigator-initiated grant mechanisms, which include the Traditional Research Grant (R01), the New Investigator Grant (R23), the Conference Grant (R13), the Program Project Grant (P01), and Small Business Innovative Research (SBIR) grants (R43 and R44). This year two new grant mechanisms have been sponsored by the National Cancer Institute, which include the Academic Enhancement Research Award (R15) and the Outstanding Investigator Grant (OIG or R35). The Division's emphasis on investigator-initiated research is based on the fact that the two largest program areas of Tumor Biology and Immunology focus strictly on basic research where progress is completely dependent upon the creative ideas of individual scientists. The smaller program area of Cancer Diagnosis, however, continues to use program initiatives in the form of RFAs to stimulate studies that link basic research findings in tumor biology and immunology to the clinic. In addition, the Cancer Diagnosis Program places greater emphasis on the use of SBIR grants, which are intended to promote basic information into the commercial arena.

There are a number of significant budget trends that we believe are reflective of changes in the scientific management of the Division and changes in the directions and emphasis of biomedical research. While the Immunology Program dollar level for FY 85 has remained stable compared to FY 84, the number of research grants supported has decreased from 444 to 395. There are a number of reasons for this change which are probably not the result of lower budgets, since the proportion of approved grants funded has not changed drastically compared to previous fiscal years. Many studies dealing with monoclonal antibodies are rapidly being promoted into the Biological Response Modifiers Program in the Division of Cancer Treatment where clinical applications can be investigated more effectively. The Diagnosis Program in DCBD has established a more effective system for promoting basic findings in immunology into the development of better diagnostic tests for cancer. Also, the National Institute of General Medical Sciences has established an immunology program which has altered the distribution of support for investigator-initiated immunology research between institutes at the NIH. Unlike the Immunology Program, the Diagnosis Program has achieved an increase in its grant portfolio of thirty per cent in the last year. This is due to increases in the number and quality of diagnostic research grant applications, an effective use of RFAs to build areas of importance, and more effective management links between the Diagnosis Program and the program areas of Tumor Biology and Immunology. The Tumor Biology Program has experienced an increase in budget and a small decrease in the number of grants supported. Much of the decrease in number of grants can be explained by the fact that the program supported

five Outstanding Investigator Grants, a new funding mechanism that consolidates all of the research previously supported by a number of grants to the same individual. Overall, the science supported by the Division is of the highest quality and the rate of discovery is progressing rapidly and effectively as new technologies such as DNA recombinant biology are used more widely.

TUMOR BIOLOGY PROGRAM

Description and Introduction

The Tumor Biology Program supports a broad spectrum of basic biological research to determine what cellular and molecular factors distinguish cancer cells from normal healthy cells and tissues. The supposition is that knowledge of these properties and processes will help us learn how to manipulate or change the biological signals responsible for the aberrant behavior of cancer cells. Ultimately, this should result in more effective methods for the diagnosis, treatment and management of cancer victims.

Within the Tumor Biology Program, there are three major areas of investigation which conveniently correspond to different theories of how to control the development and progression of neoplastic disease. The first is understanding the basic biochemical mechanisms involved in growth control, whether these involve particular external signals that initiate the process of cell division or cellular molecules more directly responsible for the control of DNA replication and metabolism. This kind of information can lead to the development of specific hormonal and drug therapies. The second is studying changes that occur at the molecular level which lead to cancer cell invasion. The invasive behavior of cancer cells is a prerequisite to malignancy, or the ability of tumors to invade surrounding tissues, escape normal host defense mechanisms and become established at multiple secondary metastatic sites of growth. Theoretically, if the invasive properties of malignant tumors can be controlled and these tumors confined to particular sites, metastasis, the major killer in cancer patients, will not occur. Treatment of tumors confined to a single site is usually more successful. The third is to develop detailed biological and biochemical information about the processes which induce cancer cell differentiation. There is good reason to believe that many kinds of cancers will respond to external stimuli and differentiate. If the genetic program of an actively growing cancer could be changed to one of terminal differentiation, then the malignant tumor could be rendered harmless. Although the above emphasis of the the Tumor Biology Program in the areas of growth, invasion and differentiation is stated in simple terms, they provide a purposeful way of viewing the role of basic biological research to the ultimate goal of curing cancer.

The kinds of information developed in the Tumor Biology Program provide a foundation for and relate directly or indirectly to nearly every other program area within the National Cancer Institute. The importance of basic tumor biology research to the National Cancer Plan is reflected by the large $73.4 million commitment of the NCI to this program area in FY 1985. (See Budget Table.) Complete listings and summaries of all grants supported by the Tumor Biology Program are included in the attached Appendices.

Scientific progress in the area of tumor biology is developing at a remarkable pace. There is no doubt that DNA recombinant technology continues to be the centerpiece of basic cancer biology research. This technology combined with other methods for introducing foreign genes into cells, especially by transfection and microinjection, has introduced experimental approaches which are yielding insightful results explaining the nature of the changes in normal cells which lead to uncontrolled growth and spread of cancer cells. The following report selectively reviews areas in which progress has been exceptional and there is considerable promise for future research.

Oncogenes and Cancer

Although research in the study of "oncogenes" continues to provide exciting and informative insights into the molecular genetics of cancer, it is important to remember that the use of the term oncogene is a misnomer because these are normal genes which play a crucial part in the biochemistry of all normal cells. Only the aberrant version or expression of these normal genes can be properly termed a cancer gene or oncogene. It must be emphasized that "oncogenes" are operationally defined as genes which act in a dominant fashion to stimulate or sustain uncontrolled growth (i.e., growth transformation). There are other ways in which to sustain neoplastic growth and there are likely to be other genes completely separate from oncogenes which contribute to tumor growth, invasion and metastasis. As we understand more about the cancer process, there is a good possibility that other terminologies such as suppressor genes, anti-oncogenes and metastasis genes will be required before the cancer process is ultimately and fully characterized in the genetic sense. While few new oncogenes have been discoverd in the last year (see appended table, "Families of onc Genes"), there has been important progress in identifying the biological activities of various oncogene products and the relationship of different oncogenes to each other in normal developmental processes and growth transformation processes. However, there still is very little known about the mechanism of action of oncogene products, which is clearly an area of research that must proceed successfully before there will be any practical benefits to medicine and the cure of cancer.

The search for new oncogenes was not particularly successful in the past year and is severely limited by the assay systems which are available for detecting transforming genes. The NIH 3T3 cell line continues to be one of the most proficient in taking up and integrating foreign DNA, the process of transfection, as well as being reasonably resistant to spontaneous neoplastic transformation. A new cell line, EL2, which spontaneously arose from primary rat embryo fibroblasts is distinctive in that it appears to be highly susceptible to a number of different transforming genes while exhibiting a low rate of spontaneous transformation (Liboi et al., 1984). The NIH 3T3 cell line has a more limited range of sensitivity to different oncogenes and exhibits a slower rate of growth of transformants under selective culture conditions. Since the 3T3 system has never been completely satisfactory, the EL2 cell line if it continues to perform well in other laboratories, may become the in vitro assay system of choice for detecting "oncogenes." Because the in vitro focus assay using NIH 3T3 cells appears to have a strong bias for the ras gene family, efforts have been made to develop a sensitive in vivo bioassay system for transforming genes based on the tumorigenecity of cotransfected NIH 3T3 cells in nude mice (Fasano et al., 1984). An in vivo assay system allows investigators to discover genes which might render 3T3 cells tumorigenic, but be unable to form a recognizable focus of morphologically altered cells in vitro. Also, it would overcome the problem of spontaneous foci in the background which obscure detection of certain transforming genes. The promise of this method is preliminarily established by the discovery of two new transforming genes, mcf 2 and mcf 3, as well as the N-ras oncogene in the human mammary carcinoma cell line, MCF-7. A similar system has been used to demonstrate that NIH 3T3 cells transformed in vitro with genomic clones of the ras oncogene express the metatastatic phenotype in nude mice (Thorgeirsson et al., 1985). While the in vivo assay

systems offer new possibilities for detecting additional growth transforming genes (i.e., oncogenes as they are currently defined) they are essential for making progress in the discovery of metastasis genes.

Experimental support for the idea that "oncogenes" serve important normal functions in both development and differentiation continues to accumulate. Although we do not know the mechanisms which control the expression of oncogenes, the temporal appearance and disappearance of oncogene transcripts and protein products provides circumstantial evidence of their critical biological roles. The expression of some of the most common oncogenes has been studied during embryonic and fetal development of the mouse (Slamon and Cline, 1984). The oncogenes c-myc, c-erb and c-src appeared to be highly regulated during embryogenesis, while c-Ha-ras and c-sis were expressed throughout all of mouse embryonic development. These results suggest a stage-specific, tissue-specific role for some oncogenes during development and differentiation and a more generalized role for other oncogenes in all normal growth processes. Considering the fact that oncogenes are conserved throughout phylogeny, these kinds of results further support the idea that the association of cellular oncogenes with the malignant state is merely a reflection of untimely or inappropriate expression of genes whose functions are central to normal growth and development. There is evidence that c-mos expression is not only highly regulated during mouse development but that there is also possible tissue-specific regulation of the size of the mos transcripts, suggesting the possibility that they could give rise to functionally different protein products in specific tissues (Propse and Woude, 1985). There have also been studies which implicate an active role for both c-sis and c-myc in the developing human placenta (Gouston et al., 1985; Pfeifer-Ohesson et al., 1984). There appears to be a role for c-myc during the proliferation of normal cells in placenta tissue, while c-sis activity not only precedes the expression of c-myc but appears to be under autocrine control during trophoblast growth. In the hematopoietic system, there appears to be active but separate roles for different oncogenes during the differentiation process, depending upon the particular cell lineage. The kinetics of expression of c-fos transcripts support the view that this gene product serves an important role in human myeloid cell differentiation (Mitchell et al., 1985; Muller et al., 1985). The special role for c-fos is further emphasized by the fact that results from other laboratories show c-myb and c-myc expression decreasing during terminal differentiation of monocytes and myelocytes when c-fos is increasing markedly (Gonda and Metcalf, 1984). Changes in c-myc expression may be important in the irreversible commitment of erythroleukemia cells to terminal erythroid differentiation (Lachman and Skoultchi, 1984). The more data that become available, the more convincing is the argument that oncogenes serve critical roles in normal growth, development and differentation.

Identification of the c-fms oncogene product represents one of the more substantial discoveries in the last year. A consistent series of results established that the v-fms gene coded for a glycoprotein product that was associated with the Golgi complex and could be detected at the plasma membrane (Anderson et al., 1984). Using a mutant of the v-fms gene that was not processed into a glycoprotein which could be detected at the cell surface, it was established that the transforming activity of the v-fms gene product was mediated through target molecules on the plasma membrane (Roussel et al., 1984). The

orientation of the v-fms coded glycoprotein was studied by proteolytic digestion. Interestingly, the v-fms glycoprotein had a transmembrane orientation, a topological feature similar to those of several growth factor receptors, suggesting that v-fms transforms cells through modified receptor mediated signals (Rettenmeir et al., 1985a). When antibodies to the v-fms glycoprotein are used to isolate the c-fms protooncogene product, it appears that the transforming activity of the v-fms gene is a truncated form of the c-fms growth factor receptor (Rettenmeier et al., 1985b). This is consistent with experiments last year which established that the erb transforming gene is a truncated version of the c-erb protooncogene which codes for epidermal growth factor receptor. Soon to be published results will clearly establish that the c-fms protooncogene product is either related or possibly identical to the receptor for murine colony stimulating factor one (CSF-1) (Sherr et al., unpublished). CSF-1 is a lineage-specific hematopoietic growth factor required for the survival, proliferation and differentiation of cells of the mononuclear phagocyte series (precursor cell ⟶ monoblast promonocyte ⟶ monocyte ⟶ macrophage). (See M-CSF under Growth and Differentiation Factors for the Hemopoietic System.) Therefore, the fms oncogene could be a critical gene involved in myeloid leukemias.

A significant proportion of human tumor cell lines and chemically induced rodent tumors contain activated ras genes capable of inducing morphological and tumorigenic transformation when introduced into preneoplastic test cell lines (e.g., NIH 3T3) by DNA-mediated gene transfer (i.e., transfection). Although nearly 20% of all human tumors contain activated ras genes, until now very little was known about the protein encoded by it and what the protein does in the cell. By direct experimentation it has been fully confirmed that the ras gene functions through a protein product, protein p21. When the oncogenic form of purified p21 is microinjected into NIH 3T3 cells, they become fully transformed (Stacey and Kung, 1984; Faramisco et al., 1984). The protooncogenic form of p21 (i.e., the normal protein) has little or no effect (Faramisco et al., 1984). The biological effects of p21 can be reversed by microinjection of antibodies to the normal (Mulcahy et al., 1985) or oncogenic (Faramisco et al., 1985) forms of these proteins. While evidence continues to accumulate that the ras gene is "activated" by mutation (Nakano et al., 1984; Zarble et al., 1985), there may now be an explanation for these findings based on new information which has identified the biological activity of the normal ras gene product. There has always been an inconsistency between the observation of mutation and the assumption of activation, since most highly conserved proteins critical to cell survival would be expected to become inactivated by mutation. Recent findings reveal that the normal p21 protein has GTPase activity and that the mutant p21 protein has very little GTPase activity but retains normal GTP binding activity (Sweet et al., 1984; McGrath et al., 1984; Manne et al., 1985). Thus, the mutated form of p21 is not an "activated" ras gene product but a protein that has had one of its normal functions "inactivated." Furthermore, the normal ras protein contains substantial sequence homology to GTP binding proteins (G proteins) which transduce signals generated by ligand binding to cell surface receptors into changes in intracellular metabolism. It has been postulated that the ras protein functions like the alpha-subunit of G-proteins, cycling through alternative configurations as a result of association with growth factor receptors and guanine nucleotides (Hurley et al., 1984). Thus, there is a strong likelihood that transforming ras proteins will turn out to function by subverting growth factor controls on cell proliferation.

The above hypothesis about the function of the ras oncogene is even further confirmed by interesting experiments which cancer researchers have conducted in yeast, a simpler eukaryote than its mammalian counterparts in which the genetics can be manipulated more easily. The first major finding of significance was the functional homology between mammalian and yeast ras genes (Kataoka et al., 1984; Terneles et al., 1985; Kataoka et al., 1985). Although yeast contain two distinct ras genes, at least one intact ras gene is essential for survival. The genes of yeast and mammals are so tightly conserved, however, that the human ras gene will function in yeast cells. Yeast cells with ras genes mutated analogously to oncogenic human ras genes lost the ability to germinate. The mutation resulted in a biochemical defect which activated protein kinase A activity continuously, indicating that the mutated ras gene is an activator of the enzyme adenylcyclase, which regulates cyclic AMP concentrations in the cell (Toda et al., 1985). Adenyl cyclase is an integral component of the system that transmits hormonal signals from the outer membrane to the cell interior. It is not too far fetched to believe that the tyrosine kinase activation in response to growth factors is linked at some point to the system involving adenyl cyclase and protein kinase A. Also, it is not surprising that other observations have resulted in the suggestion that ras oncogenes work via a pleiotropic mechanism (Yoakum et al., 1985; Spandidos and Wilkie, 1984).

The so-called p53 protein has been known for over six years because of its unusual association with the large T protein of simian virus 40 and the E16 58K protein of adenovirus. Although not closely related in structure, both of these viral proteins are involved in the oncogene action of their parent viruses. Thus, there is the implication that the p53 protein is somehow important for their action in cellular transformation. Furthermore, many transformed cell lines and primary tumor isolates contain elevated levels of p53. New discoveries suggest that alterations in p53 levels and stability in many mouse tumors may be directly involved in their altered growth. Although not as effective in complimenting ras activity as the myc gene, rat embryo fibroblasts (REF) which are not transformed by either ras or p53 alone do become transformed when ras or p53 are introduced together (Parada et al., 1984). A similar but equally convincing result was obtained with both REF cells and Chinese hamster embryo fibroblasts (Eliyaher et al., 1984). It would also appear that p53 can immortalize certain kinds of cells and increase their susceptibility to ras transformation (Jenkins et al., 1984). When an Abelson virus transformed cell-line, L12, which does not express p53, is transfected with the p53 gene, the expression of p53 gives rise to cells which produce increasingly lethal tumors in syngeneic mice (Wolf et al., 1984). Therefore, in different cell systems p53 can immortalize and transform cells, as well as act as a tumor progression factor. Although there is further evidence that genomic rearrangements which activate the p53 gene result in transformation (Mowat et al., 1985) and that p53 may play a key role in the progression of normal cells from the growth-arrested state to the actively dividing state (Reich and Levine, 1984), the precise mechanism of action and biological activity of p53 remain unknown. It is possible that this protein plays a key role in many if not all growth processes as well as in the altered control of cell division in the transformed state. A possible role for this protein in human neoplasms has not been established.

It is clear that oncogene research has become more and more intertwined with some of the most complex control processes in cell biology. The discovery that the ras oncogene alters adenyl cyclase activity, and thus the levels of cAMP in the cell, links the transformation process to the most well-studied, but still only partially understood second messenger signaling system in eukaryotic cells. Despite the implications that certain oncogenes such as c-myc are "activated" by translocations, clear genetic proof for this has proved to be contradictory and difficult to explain (Robertson, 1984). Nevertheless, continued progress in understanding both the molecular genetics and biochemistry of oncogenes has pulled together what appeared to be unrelated areas of basic research, and stimulated a resurgence of comprehensive scientific hypotheses which explain the continuum of events in biology from development and differentiation to neoplastic transformation.

Inheriting Cancer from Missing "Suppressor" Genes

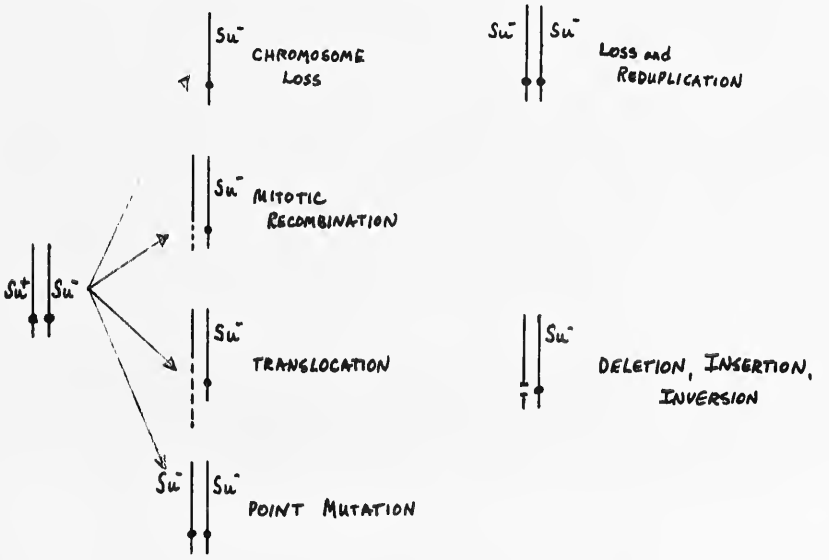
Although it has become commonly accepted that most cancers develop when cellular oncogenes are activated, there are a few extensively studied rare inherited tumors which appear to arise when certain normal genes are missing or inactive. These recessive genes appear to be responsible for a kidney tumor called Wilms' tumor and an eye cancer called retinoblastoma. While these tumors are diagnosed mostly in children and appear to develop by a new kind of mechanism, inactivation of a normal gene, there is a strong possibility that similar mechanisms are operating during the development and progression of other kinds of cancer. Unfortunately, there are no simple ways to detect the absence of unknown normal gene activity, so scientists must screen a large number of different adult cancers to look for the presence of heritable genetic traits that are similar to those associated with the development of childhood tumors. These investigations may reveal a whole new broad category of cancers.

There is strong chromosomal evidence that supports the role of a diploid pair of "suppressor" alleles, the loss of function of which is associated with the appearance of malignant retinoblastoma (Murphree and Benedict, 1984). In genetic terms an individual with no sign of cancer would be represented by a diploid gene complement of Rb^+/Rb^+, $Rb^+/rb-$ or $Rb^+/-$ while the tumor of the individual suffering from cancer would be represented by a gene complement of rb^-/rb^-, $rb^-/^-$ or $^-/^-$, where rb^- represents an inherited genetic alteration leading to inactivation and - represents a chromosome deletion responsible for inactivation. There is no doubt that individuals who have a constitutional genotype of Rb^+/rb^- or $Rb^+/^-$ are at considerably greater risk to developing retinoblastoma. In fact, more than 50% of those heterozygous individuals who have had and survived hereditary retinoblastoma are still likely to die of a non-ocular malignancy before age 35. For example, the Rb^+/rb^- survivors of retinoblastoma are at a 2000 times greater risk to osteosarcoma than the Rb^+/Rb^+ constitutional genotype. The Rb gene must be considered a powerful generalized human anti-cancer gene. Interestingly, it was the retinoblastoma studies in the early 1970's that led to the two hit hypothesis for tumorigenesis. In this case, both alleles in each chromosome must be inactivated by genetic alteration or deletion before their wild type suppressor function is completely abolished.

Although by both genetic and physical mapping the Rb locus on chromosome 13 has been implicated in the development of retinoblastoma, the rigorous proof of this hypothesis was recently obtained by specifically identifying which chromosome 13 of the diploid complement of an affected parent carried the predisposing Rb locus mutation and gave rise to retinoblastoma tumors in the children (Cavanee et al., 1985).

Like retinoblastoma, Wilms' tumor occurs in childhood in both inherited and spontaneous (sporadic) forms. In a small percentage of both forms, a specific deletion of band p13 on chromosome 11 has been observed. This deletion provides a clue as to which chromosome region might be involved in Wilms' tumor and again supports the idea that two mutational events are necessary for tumor formation (Solomon, 1984). Using a series of DNA probes that can identify differences in the sites which various restriction enzymes cut in the DNA molecule (i.e., restriction fragment length polymorphisms) it was shown that specific loci on chromosome 11 in Wilms' tumor, similar to the situation for chromosome 13 in retinoblastoma, are involved in tumorigenesis. In cases where normal tissue was heterozygous (i.e., WT^+/WT^-, $WT^+/-$), the tumor is often homozygous (i.e., WT^-/WT^-, $WT^-/^-$ or $^-/^-$) Thus, it was clearly shown that there was a functional loss of the Wilms' locus in the tumor on both chromosomal alleles by mutation, deletion or chromosome loss (Koufos et al., 1984; Fearon et al., 1984; Orkin, 1984). There is also evidence which supports the hypothesis that in some cases WT locus inactivation results from a translocation (Reeve et al., 1984).

There are a number of mechanisms which could lead to homozygosity of a recessive allele in the diploid genome that can explain how inactivation of a suppressor gene (Su) might occur. If Su^+ is the wild type gene, Su^- is the mutated gene and - is the deleted gene, the following possibilities can occur beginning with a heterozygous individual who is at high risk:



As more DNA probes are developed from the human genome and more knowledge is acquired about the human gene map, the possibility of identifying the specific mechanisms leading to the recessive phenotype will be improved. The precedent has now been established in the retinoblastoma system that restriction fragment length polymorphism (RFLP) analysis is an important tool in the study of gene inactivation. The development of recombinant DNA probes for RFLP analysis of other chromosomes should prove useful in studies of the expression of other recessive alleles in other genetic predisposition systems and in the analysis of the roles played by single genes in tumorigenesis and tumor progression.

The idea that there may be a large proportion of cancers which develop because of the "inactivation" of suppressor genes should not be overlooked. Along with the discovery of "activated" oncogenes by DNA transfection studies has emerged the tacit assumption by many scientists that dominantly acting cellular genes are responsible for the cancerous state. Recent and past research using intra- and interspecific somatic cell hybrids between normal and malignant cells continues to emphasize that there are regulatory genes in normal cells which suppress the tumorigenic phenotype (Stanbridge et al., 1983; Stanbridge, 1984; Feo et al., 1985; Stoler and Bouck, 1985; Klinger and Shows, 1983; Craig and Sager, 1985). It may be much more prudent to support the idea that the neoplastic/malignant phenotype is a complex balance between genetic elements which have expressor functions (i.e., oncogenes) and suppressor functions (e.g., Rb^+ and WT^+). The fact that suppressor genes are more difficult to identify biologically and molecularly should not cloud the view that they may serve a major regulatory role in controlling the development of many forms of cancer.

Gene Amplification and Tumorigenesis

It has been well-established that during evolution certain critical genes in cells are duplicated. This has been demonstrated both in prokaryotes (e.g., bacteria) and eukaryotes (e.g., man), but perhaps the most well known example of gene duplication is the amplification of ribomosomal DNA (i.e., r-DNA). The selective amplification of copies of r-DNA is one way which virtually all organisms have found to ensure uninterrupted expression of a gene critical to an essential biochemical process (i.e., protein synthesis). Increasing gene dosage via gene amplification not only modulates the level of expression of a given gene, but can also explain some types of evolutionary selection where a single gene is amplified and the amplified copies diverge genetically over time. For example, recently it has been postulated that normal genes such as alpha-fetoprotein and albumin were derived from a common ancestral gene (Alexander et al., 1984). Therefore, gene amplification is a normal process in nature.

Tumors and tumor cells are particulary capable of amplifying genes, and there is increasing evidence that gene amplification is not only responsible for the acquisition of tumor cell drug resistance, but is also an important factor involved in tumor progression (Schimke, 1984). When gene amplification was reviewed in our Tumor Biology report of FY 1982, there were a number of

indications that understanding the process would be important for understanding many aspects of tumor biology. At that time, it was clearly established that two types of karyotypic abnormalties were associated with gene amplification in tumor cells and transformed cell lines: (1) homogeneous staining regions (HSRs) and (2) double minutes (DMs). It was clearly demonstrated that "acquired resistance" of tumor cells to drugs was the result of amplification of specific metabolic genes. Furthermore, gene amplification occurred in situations other than those involved in drug resistance and different genes were amplified in different tumor cells. But the genes amplified in tumor cells not exposed to selective agents remained unknown. In every case, however, gene amplification was accompanied by the presence of HSRs and DMs.

HSRs are regions at the end of or within an intact chromosome that consist of multiple copies of the same DNA sequence but fail to exhibit the differential staining patterns characteristic of banded chromosome preparations. DMs are extrachromosomal entities visible during the metaphase stage of mitosis, lack centromeres, and unlike HSRs are distributed randomly to daughter cells after mitosis. DMs are unstable and are rapidly lost when cells grow in the absence of a selective agent (e.g., a drug). The process of gene amplification in tumor cells is often associated with the movement of amplified DNA sequences in DMs to different regions within the genome as HSRs. Generally, genes amplified in the form of HSRs are stably maintained in the absence of any known selective pressure and are transmitted equally to all cell progeny. HSRs are usually located at a different loci of the same chromosome or on different chromosomes relative to the non-amplified homologous DNA sequence. Clearly, gene amplification in the form of HSRs provides a possible way for tumor cells to stably adapt to their surroundings and increase their chances for survival in a hostile environment.

A growing body of information suggests that the genes predominantly amplified in tumors and tumor cells are oncogenes. Thus, again different areas of cancer genetics are converging to provide more consistent, unified interpretations of what were previously considered unrelated phenomenon. The following observations have been made in the last year:

(1) cDNA clones complementary to the c-Ki-*ras* cellular oncogene have been used to demonstrate that in Y1 mouse adrenal tumor cells, the c-Ki-*ras* gene is amplified both in the form of DMs and HSRs. This amplification results in increased expression of the *ras* oncogene and is likely to be a key factor contributing to the cancer cell phenoytype (George et al., 1984).

(2) The N-*myc* oncogene was first detected in the amplified DNA of a number of neuroblastoma cell lines (Schwab et al., 1983). Since its discovery, N-*myc* gene activation has been confirmed in two human tumors of neuroectoderm origin, neuroblastomas and retinoblastomas, but more importantly, the degree of gene amplification of N-*myc* is correlated strongly with malignant progression, being amplified greater at the advanced stages of the disease when clinical prognosis is least hopeful (Marx, 1984; Brodeur et al., 1984; Kohl et al., 1984; Schwab et al., 1984; Lee et al., 1984). The working model is that N-*myc* activation plays a primary role in the initiation of uncontrolled growth while N-*myc* amplification is a later event linked to tumor progression toward stages of increased malignancy.

(3) The c-myc oncogene has been observed to be amplified in mouse tumor cells derived from an osteosarcoma (Schwab et al., 1985) as well as in human gastric adenocarcinoma cells maintained as solid tumors in nude mice (Shikuya et al., 1985). In each situation enhanced c-myc expression was confirmed directly by detection of substantially increased levels of c-myc messenger RNA and protein. In the gastric cancers the degree of c-myc amplification was implicated in tumor progression by the demonstration of greater gene amplification and expression in the more rapidly growing, poorly differentiated tumors. Past studies have shown c-myc to be amplified in human promyelocytic leukemia (Dalla-Favera et al., 1982), human colon cancer (Alitalo et al., 1983) and human lung cancer cell lines (Little et al., 1983). Clearly, the amplification of c-myc is not limited to cancers of specific embryonic origin which appears to be the case for N-myc.

(4) The erb-B oncogene which codes for a truncated form of the EGF receptor is amplified in A431 epidermoid carcinoma cells (Ullrich et al., 1984) and in primary human brain tumors of glial origin (Libermann et al., 1985).

(5) The c-myb oncogene is amplified in both human colon carcinoma (Alitalo et al., 1984) and human acute myelogenous leukemia (Pelicci et al., 1984). The expression of c-myb in colon carcinoma was a surprise because it had previously been observed only in cells of hematopoietic origin. Furthermore, even more startling was the fact that c-myb amplification was located on redundant copies of the same abnormal chromosome, not as DMs or HSRs. These findings emphasize the possibility that amplification of DNA need not manifest itself in cytogenetic analyses and raise the possibility that amplification of cellular oncogenes may be a more common factor in tumorigenesis than might have been suspected from karyological data. In the study of gene amplification of c-myc and now c-myb in AML cell lines, it is apparent that two phenotypically similar tumors express alternately either c-myc or c-myb but not both. This suggests that tumor subtypes that are indistinguishable by current morphological or biochemical techniques may be characterized by different genetic markers which may be helpful in the design of more effective therapies.

There appears to be little doubt that gene amplification is a characteristic feature of many different kinds of human primary tumors and tumor cell lines. There are several examples which correlate enhanced expression of oncogenes resulting from gene amplification to progressively malignant stages of cancer. The fact that gene amplification has been observed for all classes of oncogenes suggests that this process is of fundamental importance to neoplasia. While the precise mechanism(s) responsible for gene amplification remains undefined, the development of new techniques for studying amplified DNA sequences (Roninson et al., 1984) and the increasing interest of many different laboratories in this process is sure to provide substantial progress in the future.

Transgenic Mice - New Experimental Systems for Cancer Research

Despite all of the incredible advances in molecular biology and immunologic technology until now there has been no way for cancer researchers to manipulate the genetic make-up of animals for the purpose of studying tumor biology. The use of transgenic mice, where specific genes are introduced into the heritable germ line, offers the possibilities of investigating the effects of specific genes in the development and progression of cancer in whole animals. The number of basic research studies in transgenic mouse systems have expanded rapidly in the last year. Once it was demonstrated that specific genes accompanied by their control flanking DNA sequences were expressed in the transgenic mouse in a tissue-specific fashion, a major obstacle in the use of genetically engineered mice was overcome. Transgenic mice are one of the best examples of how combining developing technologies offers new and important experimental opportunities for tumor biologists. These technologies are DNA recombinant biology for the isolation of "oncogenes," microinjection techniques for introducing foreign genes into fertilized eggs, and implantation technology to ensure normal development of fertilized eggs in the mother's womb. Other than the fact that all observations of experiments in whole animals will have undeniable relevance to *in vivo* physiology, there are a number of advantages to experimental transgenic mouse systems: (1) a gene of known origin and sequence becomes inserted into the germ line and thus is present in the same chromosome location of every cell in the animal's body; (2) the gene can be retrieved whenever necessary to see what modifications it has undergone in different tissues; (3) sequential changes in gene DNA structure and expression can be studied in different tissues during the development and aging of the animal; and (4) the genetic elements which dictate tissue-specific or cell-specific expression of genes can be studied.

The first experiments using transgenic mice for cancer research have been accomplished and have fully verified the potential of this experimental approach. In normal cells, c-*myc* oncogene activity is repressed and there is no danger of developing cancer. However, when the normal coding sequences of c-*myc* are linked to the regulatory sequences of mouse mammary tumor virus (MMTV) and the fused genes introduced into fertilized mouse eggs, the resultant progeny female mice are prone to the development of distinctive adenocarcinomas of the breast tissue (Stewart et al., 1984). Since the MMTV control sequence used responds to lactation hormones, especially glucocorticoids, by stimulating expression of the gene to which it is connected, the association between lactation and tumor formation is not unexpected. Of the 13 strains of transgenic mice developed, expression of the fused genes varied among the different animals, but a number of important observations and conclusions can be made from the best studied of these strains. First, both tumor and normal breast tissue expressed high levels of RNA transcripts corresponding to the fusion gene. Therefore, c-*myc* contributes to but is not sufficient for the development of cancer, which is *in vivo* confirmation of what has been called the multistep carcinogenesis process. Second, these results confirm the notion that c-*myc* in the human genome, in its normal position on chromosome 8, is repressed by some unknown mechanism and that activation of the gene can be achieved genetically by moving it to a chromosomal site which allows enhanced expression. Third, the increased expression of the oncogene is not necessarily deleterious to development.

If a viral transforming gene is fused with the mouse metallothionein gene regulatory sequences and introduced into the germ line of mice, a high percentage of the transgenic mice develop brain tumors (Brinster et al., 1984). Like the c-myc experiments, this simian virus (SV) 40 T-antigen transforming gene did not interfere with normal development. However, although the choroid plexus tumors and cell lines derived from them contained significant levels of SV40 T-antigen and its corresponding message, no expression was detected in total brain tissue prior to tumorigenesis. The hybrid metallothionein -oncogene is somehow inactivated in development in some stable but reversible manner. It could have been postulated that the SV40 early region genes would contain special DNA sequences called enhancer elements which would confer brain tissue specificity of expression. However, since normal brain tissue adjacent to the tumor fails to express the SV40 T-antigen the events leading to tumorigenesis in this situation must be different than those leading to the formation of adenocarcinomas in the transgenic mice described previously. A closer examination of the tumors and cell lines derived from these tumors revealed that they contained amplified SV40 sequences, again indicating the need for a second genetic change before increased expression and tumorigenesis can take place.

The heritable formation of pancreatic B-cell tumors has been demonstrated in transgenic mice carrying a hybrid insulin-SV40 gene (Hanahan, 1985). In this case the DNA sequences associated with the insulin gene which dictate tissue and cell-type specific expression are fused with the transforming SV40 large T-antigen gene. When the hybrid gene is expressed in transgenic mice, it is present in all insulin producing B cells, but tumors are produced only after a long latent period in some of the B cells. These results suggest, as in other transgenic oncogene studies, that increased oncogene expression in vivo is a necessary but not a sufficient condition for tumor formation.

The use of transgenic mouse models will permit the investigation of very complex biological phenomenon at a level of molecular understanding that previously was not possible. Clearly, insertion of oncogenes, of either viral or cellular origin, into the germ line provides in vivo systems in which the mechanism of tumorigenesis can be analyzed and which is also likely to facilitate the study of development, differentiation and cellular interaction. The further delineation of the "control elements" in eukaryotic genes will be a key factor in the design of molecular DNA hybrid molecules which will have increasingly specific biological effects.

Steroid Hormones and Gene Regulation

The steroid hormones are a class of structurally similar molecules that, according to "central dogma" evoke cellular responses by a universal mechanism - they form complexes with their specific cellular protein receptors which then become "activated" and in turn promote the transcription of sensitive genes. The study of the action of these steroid hormones at a molecular level thus becomes the study of the hormone receptors. And specific though each may be, there are remarkable parallels among the structures of receptors for estrogens, progestins, androgens, mineralocorticoids and glucocorticoids in a wide variety of tissues (Sherman and Stevens, 1984). From the point of view of cancer biology

however, there are two important categories of steroids that are especially relevant, the sex steroids including the estrogens and androgens that can act as tumor promoters in sensitive target tissues and the glucocorticoids which are normally immunosuppresive and are used therapeutically because they kill malignant lymphocytes. In the past several years some interesting new developments in steroid receptor biology in these various systems have been reported that seem to be getting closer to definitive information about the nuclear events that sometimes paradoxically lead to the synthesis of new proteins and to the disappearance of others, and that induce proliferation in some cells and cause cytolysis in others.

For fifteen years there had been a consensus for the "two-step" hypothesis for estrogen action: first, the hormone bound to an inactive cytoplasmic receptor, then the active complex was translocated to the nucleus. However, in the past year this concept has changed drastically with several publications which show that even the unoccupied receptor is concentrated in the nucleus (Schrader, 1984; Welshons et al., 1984; King and Greene, 1984). The receptor may be permanently anchored like a weakly bound non-histone nuclear protein, and the interaction with estrogen within the nucleus must result in a subtle change in the receptor which increases its affinity for DNA and provokes important responses. Whether or not re-examination of the receptors for other steroid hormones will modify the view of their mechanism of action remains to be seen.

One of the best known estrogen-dependent systems is the mammary epithelial cell. Early assessment of estrogen receptors in human breast cancer is an important diagnostic tool, since the loss of dependence on estrogen is consistent with the most aggressive tumors. Recent information on a human breast tumor cell line (MCF-7) which has estrogen receptors and normally requires estrogen for tumorigenicity *in vivo* demonstrates that the cell line can be made totally independent of any estrogen requirement. When MCF-7 cells were transfected with the oncogene Harvey *ras*, the oncogene was expressed and the cells grew in ovariectomized mice and formed tumors. By some yet unknown mechanism the oncogene bypassed all the intermediate steps and signals usually involved in an estrogen response (Kasid et al., 1985).

Investigations at the molecular level have not yet been carried out in any androgen-responsive systems, in part because of limited availability of androgen-dependent cell lines and tissues. The rat ventral prostate is the major experimental model for studies of androgen action, and in line with the universal hypothesis, the presumed critical androgen receptor has been partially purified from this system. Focus of this research has been on the activation of protein kinases by androgens which phosphorylate nuclear proteins including the androgen receptor. It has been reported that there are elevated levels of androgen receptor in prostatic carcinoma (Goueli et al., 1984), so the pursuit of this research may be an important direction for cancer biology.

There is no doubt but that the major developments in understanding steroid hormone action have been provided by studies with glucocorticoid-sensitive systems (King, 1984). Some answers to very difficult questions seem near: What is the structure of the glucocorticoid receptor? How is the receptor gene organized and regulated? What is the physical nature of the steroid-receptor complex

and how does it switch genes on? How do different steroid hormones influence the same cellular function? How can a single steroid hormone have different types of effects in different cells?

Several important breakthroughs have advanced research in this area. They are the production of the first successful antisera and monoclonal antibodies to glucocorticoid receptor which have helped purify this very scarce receptor protein to near homogeneity and to begin to characterize it. Both the steroid-binding and DNA binding domains of the protein have been identified (Gametchu and Harrison, 1984). The cloning of cDNA for both the rat receptor protein (Meisfeld et al, 1984; Yamamoto, 1985) and the human steroid receptor protein (Weinburger et al., 1985) have recently been reported. Also a number of variant lymphoma cell lines which do not respond to glucocorticoids have been produced that can provide a test of the biological relevance of certain molecular interactions. Studies on resistant murine cells suggest that the receptor transcripts are present but that they appear qualitatively and quantitatively different from the wild type. Certain strains of the model human leukemic cell line CEM-C7 aquire glucocorticoid resistance as a result of a somatic mutation within the receptor locus (Thompson et al., 1983). However, recent evidence suggests that cells selected *in vivo* for apparent glucocorticoid resistance (meaning they survived a regimen of glucocorticoid treatment) may not exhibit steroid resistance *in vitro*. In many cases they have normal receptor levels which are also functionally normal and can induce certain glucocorticoid responses. This is an especially important problem in predicting clinical responses to glucocorticoid therapy for malignant lymphoid cells (Munck and Crabtree, 1981; Wood and Thompson, 1984).

The third important development in studies on the mechanism of glucocorticoid receptor action is the clever use of the mouse mammary tumor virus (MMTV). MTV is one of several genes (including mouse metallothionine and rat growth hormone), the transcription of which is induced by glucocorticoids, thus, any cell can be simply infected with MTV and the appearance of viral transcripts can be monitored as an indicator of steroid responsiveness of the cell. Experiments *in vitro* with purified steroid receptor now indicate that this transcription is switched on by the binding of receptor to at least five specific DNA regions both outside (upstream) and inside the MTV gene. Within each region are multiple binding sites each including a highly conserved octanucleotide. These same sites (called glucocorticoid response elements or GREs) also appear responsible for receptor interaction in cultured cells (Yamamoto, 1985).

Another example is the transcription of the lysozyme gene, regulated *in vivo* by both glucocorticoid and progesterone. In this case the receptors for the two different hormones seem to bind overlapping DNA sequences upstream from the gene. Unfortunately, these kinds of direct experiments are not yet possible with estrogen receptor because there are no model estrogen-inducible genes that can be exploited.

Although the type of physical-chemical bonding that actually occurs between the glucocorticoid receptor protein and the DNA sequences has not been determined, it results in the appearance of DNase hypersensitve regions. This suggests a change in the chromatin configuration that allows the entry of polymerase and permits transcription.

The explanation of how glucocorticoids turn on genes seems straightforward enough. Then consider another function of glucocorticoids, the inhibition of proliferation of cells such as murine thymic lymphosarcoma cells. Turning genes off probably requires a more complex and indirect mechanism of action. It has been proposed that in these cells the activated glucocorticoid-receptor complex interacts with the genomic sequences that encode a special rDNA initiation factor designated as TFIC that is critical to ribosomal synthesis and in this way suppresses transcription of the factor and all subsequent steps (Cavanaugh et al., 1984). Another example of the diverse effects of glucorticoids (actually the glucocorticoid receptor!), presumably also at the genetic level, is the rapid and dramatic decrease in plasminogen activator (PA) in a rat hepatoma cell line within an hour or two of exposure to the steroid. Recent evidence shows that glucocorticoids (dexamethasone) inhibit PA activity by inducing the synthesis of a specific PA inhibitor without decreasing the amount of PA protein (Cwikel et al., 1984). No doubt other secondary factors that act as inducers, messengers or even inhibitors will be implicated in what has to be a complex process of gene regulation and cellular growth. And the steroid hormones are only one piece of this fascinating program.

Cell Surface Membrane Alterations in Malignancy

Mammalian cell membranes are basically composed of protein, lipid and carbohydrate. The carbohydrate is either conjugated with protein (glycoproteins) or lipid (glycosphingolipids), with the vast majority of these conjugates being glycoproteins. Since cell-cell interactions are probably mostly controlled by cell surface specificities and there is evidence for molecular changes in cell surface moieties during malignant transformation, elucidation of these changes is of particular interest to tumor biologists. To understand malignant transformation, it is also important to delineate changes in cell surface glycoproteins and carbohydrate antigens during normal cell development, e.g., erythropoiesis. One change that has been noted during erythropoiesis is in cell surface lactosaminoglycan (Fukuda and Fukuda, 1984). Lactosaminoglycan is a class of glycoprotein - or glycolipid-linked carbohydrate chain (long-chain oligosaccharide) found in Chinese hamster ovary cells, Friend erythroleukemic cells and mouse embryonic cells as well as human erythroid cells. The long chain glycolipids and some carbohydrate chains on fetal erythrocytes contain a linear unbranched version of lactosaminoglycan, which is converted to a highly branched structure several months after birth. Since lactosaminoglycan carries blood group determinants, changes in its structure alter the status of these antigens, suggesting that lactosaminoglycan plays a crucial role in the regulation of expression of cell surface glycoproteins, and possibly regulation of gene expression for proteins such as hemoglobin. Others have also observed cell surface glycoprotein alterations in normal and malignant hematopoietic differentiation and are pursuing the hypothesis that some of these changes are due to different glycosylations of common polypeptides (Gahmberg et al., 1983).

Because of the numerous roles that glycoconjugates play within the membrane environment, there is intense scientific interest in the effects of altered glycosylation which may in turn affect biosynthesis, degradation, compartmentalization or conformation of membrane molecules. Eighteen glycosylation mutations of Chinese hamster ovary cells, obtained by selection for resistance to cytotoxic

plant lectins, have been identified. These membrane mutants appear to arise from mutations in different genes (Stanley, 1985). Altered glycosylation of membrane glycoproteins have been demonstrated in NIH 3T3 cells transformed by transfection with DNA from human neuroblastoma and bladder carcinoma cell lines (N-ras and c-H-ras-1 oncogenes respectively), producing the hypothesis that this altered glycosylation may be necessary for the transformed phenotype (Santer et al., 1984). Other studies with neuroblastoma cells have led to the proposal that eukaryotic cell surface glycoconjugates may have a role in DNA replication (Basu et al., 1983). A novel fucoganglioside, 6B, has been isolated; it is seen in human colonic adenocarcinoma but not normal colonic mucosa by screening with a monoclonal antibody designated FH6 (Fukushi et al., 1984).

Extensive observations have been made in the field of alteration of glycoproteins on cell surface membranes. While the significance of the consistently observed changes in glycoproteins during malignant transformation is not known, it has been hypothesized that they may confer upon a cell the ability to adapt to a broad range of conditions within which the cell can operate, as a sort of environmental buffer with the bound carbohydrates being an interface between genetic and environmental influences (Warren et al., 1983; Warren and Cossu, 1983a,b).

Sialic acid is thought to play a role in communication between cells and thus the regulation of cell surface sialic acid is a subject of intense scientific interest. One way sialic acid metabolism has been studied is in sublines of the 13762 rat mammary adenocarcinoma (MAT-B1 and MAT-C1). These two cell lines show marked differences in their ability to be transplanted into mice, agglutinability with concanavalin A, and morphology. In comparing MAT-B1, MAT-C1 and a third variant for sialic acid content of a major sialo-glycoprotein (ASGP-1) and xeno-transplantability, no correlation was found (Howard et al., 1982). Nor is the three fold increase of ASGP-1 sialic acid content of MAT-C1 as compared to MAT-B1 accounted for solely by differences in the sialyltransferase of each line (Pratt and Sherblom, 1984). Other aspects of sialic acid metabolism are being pursued to explain these observations.

Investigations of this nature will enable us to elucidate how control of differentiation varies between normal and tumor cells. For example, are tumor cells arrested at a particular developmental point? These molecular changes have immediate application in diagnosis and therapy, in terms of classifying tumors. These findings imply that tumor cells can be selectively removed for therapeutic purposes, e.g., from the bone marrow of a leukemic patient. Numerous studies of mammalian cell surface changes are ongoing with various animal and human systems. Oncogenic transformation of cells alters the chemical composition and organization of cell surface membranes both in vitro and in vivo. The type of changes observed are blocked glycolipid synthesis, neosynthesis, altered contact response and changes in organization. These have been well summarized in a recent review (Hakomori, 1983). In virally transformed cells these surface membrane changes may be the result of transforming gene activation (i.e., oncogenes).

While our knowledge of the basic function of glycolipids is fragmentary, current evidence suggests that they are involved in cell recognition and/or regulation of membrane receptor function as two possible roles. There is a

clear need for more experiments to try to establish the relationship between glycolipid changes and the mechanism of oncogene activity and differentiation. As more connections are made between malignant transformation and cell surface modifications, significant advances in cancer diagnosis and therapy can be anticipated. The studies described above and related ones represent the beginnings of insight into these complex connections.

Growth and Differentiation Factors for the Hemopoietic System

It was stated last year in this Report that the protein factors responsible for the growth and differentiation of the cells of the hemopoietic system were poorly characterized as compared to various growth factors for other cell types. This was attributed to the lack of highly purified factor preparations. In the past year, however, important progress has been made in purifying and cloning the genes for two human factors and the cloning of several factors from the mouse.

The possibility of using hemopoietic growth and differentiation factors for leukemia therapy is sound because these tumor cells show an absolute dependence on these factors *in vitro*. As a form of chemotherapy these regulators could be expected to induce terminal cell differentiation of leukemia cells in a highly specific way, and to suppress stem cell renewal.

The nomenclature developed to identify these various glycoprotein factors is confusing since they are identified by the *in vitro* response that they induce, and individual multi-potential stem cells can give rise to all of the different cell types of the hemopoietic and lymphoid systems. In the mouse these regulatory factors are loosely grouped as erythropoietins, T-cell growth factor (called IL2) and a large class of colony stimulating factors which regulate the proliferation, commitment and differentiation of hematopoietic cells. This latter group includes G-CSF and M-CSF which stimulate formation of granulocytes and macrophages respectively, GM-CSF which induces formation of both cell types in bone marrow cultures, and multi-CSF (also known as IL3) that stimulates both granulocytes and macrophages, and eosinophils, megakaryocytes, erythroid and mast cells and supports proliferation and differentiation of stem cells. These colony stimulating factors have been purified from mouse leukemia cell lines and normal mouse spleen and lung, thus the site of synthesis of real physiological significance is unclear.

GM-CSF and multi-CSF of the mouse have now been cloned and expressed in COS monkey cells (Dunn et al., 1985), and each shows equivalent biological activity to the native factors. They have no significant homology between them despite their rather similar activities and similar molecular weights. Mouse G-CSF has been purified to homogeneity (Nicola and Metcalf, 1984), but has not yet been cloned. The molecular weight of 25,000 is similar to that of the other factors. This factor is the most potent inducer of terminal differentiation and profoundly suppresses leukemia stem cell renewal. The last of the group, M-CSF, also called CSF-1, was reportedly purified several years ago (Stanley, 1979), but has not yet been cloned. The receptor for this factor may be related to the *fms* oncogenes. (See under Oncogénes and Cancer.)

The establishment of a permanent T-lymphocyte cell line from a hairy-cell leukemia patient, called Mo, several years ago by Golde and co-workers, has greatly facilitated the purification of human hemopoietic growth and differentiation factors comparable to some of those seen from mouse tissues (Groopman et al., 1984). Called lymphokines in this case, since they are derived from a lymphoid cell line, Mo cells produce GM-CSF of similar activity as in the mouse, a neutrophil migration-inhibitory factor (NIF-T), a factor with erythroid-potentiating activity (EPA), a fibroblast growth factor, gamma interferon, a macrophage migration-inhibitory factor and a macrophage activating factor. Again the factors are named for the in vitro responses they provoke. Currently, two factors have been purified to homogeneity, cloned and expressed in COS monkey cells. They are the GM-CSF (Gasson et al., 1984; Wong et al., 1985) and the erythroid potentiating activity (Gasson et al., 1985). An interesting development with GM-CSF was the demonstration that both the induction of differentiation of bone marrow stem cells into differentiated granulocytes and mononuclear phagocytes and the ability to inhibit migration of human peripheral blood neutrophils reside in a single glycoprotein of molecular weight 22,000. This human T-cell GM-CSF is about 60% homologous with the mouse GM-CSF just described.

Erythroid burst promoting activity describes the ability of primitive erythroid precursors to produce large numbers of hemoglobinized cells in vitro. The factor that induces that activity is EPA (erythroid potentiating activity) which has also been purified from Mo cells which produce it. The gene has also been cloned and expressed in both COS cells and Chinese hamster ovary cells. The molecular weight is 28,000. There is no homology of protein sequence with any murine factors or with the Mo cell GM-CSF. The physiological functions of EPA are unknown. So far there has been no convincing evidence published that leukemia cells of mouse or man synthesize a unique CSF that can be linked directly to cancer. The new availability of these purified factors will now allow rigorous study of these hemopoietic regulators to address this question and how they might be exploited in cancer therapy.

Human Tumor Necrosis Factor

So much public attention has been paid to Tumor Necrosis Factor (TNF) in the past year that a brief review of the state of research on this factor seems appropriate in this report. The original observation of TNF was made just ten years ago (Carswell et al., 1975) in a report that bacillus Calmette-Guerin (BCG) infected animals, who were subsequently treated with endotoxin, produced a substance in their serum that had tumor-killing activity. When such sera was administered to mice bearing methylcholanthrene-induced sarcomas, the tumors underwent extensive hemorrhagic necrosis, without any side effects on the mice.

A number of investigators have attempted to isolate and purify native TNF, but clearly the lack of purified factor has been the major barrier to more aggressive investigations of its structure, functions and mechanism of action. TNF isolated from rabbit serum has a molecular weight of 39,000-55,000; however, the human factor has now been cloned in E. coli which expresses TNF as a protein of about 17,000 molecular weight (Pennica et al., 1984 and Wang et al., 1985).

A number of cell types have been shown to produce TNF including B-cell lines infected with Epstein-Barr virus, cells of macrophage lineage and HL-60 cells. The mechanism of action of TNF is unknown but it shows a relatively broad activity on mammalian cells of different species. It is also not known if TNF binds to cell surface high affinity receptors. In vitro, TNF, both native and the recombinant form, is cytotoxic for a number of human tumor cell lines: melanoma, breast carcinoma (MCF-7), lung carcinoma, colon carcinoma and fibrosarcoma lines. HeLa cells are not affected, and cells derived from normal tissues are TNF-resistant. Within forty-eight hours of treatment of a nude mouse carrying a transplanted human breast carcinoma, necrotic activity was apparent on the tumor's outer surface.

Now that human TNF has been cloned by several biotechnology companies, investigation of its activity and ultimately its therapeutic potential should proceed quite rapidly. Certainly TNF is the kind of biological response modifier that warrants close scrutiny (Baglioni et al., 1985).

Summary

This overview of the Tumor Biology Program emphasizes the molecular genetics of cancer cells because progress in this area has been so dramatic and because research of this kind is currently dominating scientific journals and meetings. However, as has been described, the genes themselves do not transform cells nor induce aberrant growth. The proteins produced from the genetic template must be expressed before the cell takes on the phenotype of a tumor. In the past, research progressed such that some cellular activity was described, the responsible protein was isolated, the appropriate mRNA studied and the gene finally cloned. Currently, research is proceeding in the opposite direction. Researchers start with the gene and then look for the metabolic or synthetic activity coded for by the genetic information. Since the expression of oncogenes seems to have different effects in different cell types the difficulty of this approach is even more apparent.

The new information we anticipate in the next year or two will be the result of focused investigations in protein chemistry, enzymology and cell biology. At the same time, the broad spectrum of cancer biology projects supported through this Program will undoubtedly develop new leads, new model systems, new probes, and new technology to continue to pursue the complex interactions of a cancer cell.

Families of onc Genes

Nomenclature*	Original Identification	Cellular Location
IA Tyrosine kinase activity		
src	Rous sarcoma virus (chicken)	plasma membrane
fps, fes	Fujinami sarcoma virus (chicken, cat)	cytoplasm
yes	Yamaguchi (Y73) sarcoma virus (chicken)	?
ros	UR2 sarcoma virus (chicken)	cytoplasmic membrane
abl	Abelson murine leukemia virus	plasma membrane
fgr	Gardner-Rashed feline sarcoma virus	?
IB Nucleotide sequence homology to tyrosine kinase genes - activity unknown		
mos	Moloney sarcoma virus (mouse)	cytoplasm
rel	Reticuloendotheliosis virus strain T (turkey)	?
fms	McDonough feline sarcoma virus	plasma membrane
raf	murine transforming virus	(CSF-1 receptor) ?
erb-B	Avian erythroblastosis virus (chicken)	plasma membrane (EGF receptor)
mht	Avian carcinoma virus (MH2)	?
mil	Avian carcinoma virus (MH2)	?
II GTP/GDP binding activity		
H-ras	Harvey sarcoma virus (rat)	plasma membrane
K-ras	Kirsten sarcoma virus (rat)	plasma membrane
has/bas	Balb/c sarcoma virus (mouse)	plasma membrane
N-ras+	human neuroblastoma	?
III DNA binding activity		
myc	myelocytomatosis virus MC29 (chicken)	nuclear matrix
N-myc+	human neuroblastoma	?
myb	avian myeloblastosis virus (chicken)	nuclear matrix
EIA	Adenovirus (DNA virus) (human)	nucleus
Large T	Polyoma virus (DNA virus) (human)	nucleus
fos	FBJ osteo sarcoma virus (mouse)	nucleus
IV Growth factor activity		
Blym+	human bursal lymphoma	transferrin homology
sis	Simian sarcoma virus (woolly monkey)	PDGF
erb-B	See$_B$	EGF receptor

Nomenclature*	Original Identification	Cellular Location
Other - no known activity		
mam+	mammary carcinoma (man, mice)	?
neu+	neuroblastoma, glioma (rat)	homology with erb-B
ski	Avian SK V770 virus	?
int-1	mouse mammary tumor virus	?
erb-A	avian erythroblastosis virus (chicken)	cytoplasm/potentiates effects of erb-B/ homologous with carbonic anhydrases
Middle T	polyoma virus (mouse)	plasma membrane
met+	chemically transformed human cell line	?
mcf2+	human mammary carcinoma	?
mcf3+	human mammary carcinoma	?
p53+	complexes with SV40 large T protein	plasma membrane

* All of these acronyms are expressed as v-onc or c-onc depending upon whether a viral or cellular transforming gene is being studied.

\+ Identified by transfection - no v-onc counterpart yet identified.

REFERENCES

Alexander, F., Young, P.R., and Tilghman, S.M. Evolution of Albumin: Alpha-Fetoprotein Ancestral Gene from the Amplification of a 27 Nucleotide Sequence. J. Mol. Biol., 173:159-176, 1984. (CA 28050)

Alitalo, K., Schwab, M., Lin, C.C., Varmus, H.E., Bishop, J.M. Homogeneously Staining Chromosomal Regions Contain Amplified Copies of an Abundantly Expressed Oncogene (c-myc) in Colon Carcinoma. Proc. Natl. Acad. Sci., USA, 80:1701-1711, 1983.

Alitalo, K., Winquist, R., Lin, C.C., Chapelle, A., Schwab, M. and Bishop, J.M. Aberrant Expression of an Amplified c-myb Oncogene in Two Cell Lines from a Colon Carcinoma. Proc. Natl. Acad. Sci., USA, 81:4534-4538, 1984.

Anderson, S.J., Gonda, M.A., Rettenmier, C.W. and Sherr, C.J. Subcellular Localization of Glycoproteins Encoded by the Viral Oncogene v-fms. J. Virology, 51:730-741, 1984.

Baglioni, C. et al., submitted, 1985 (CA 29895).

Basu, S., Bhattacharya, A. and Basu, M. The Role of Eucaryotic Cell Surface Glycoconjugates in DNA Replication. J. Biosci., 5:157-163, 1983. (CA 14764, CA 33751).

Brinster, R.L., Chen, H.Y., Messing, A., van Dyke, T., Levine, A.J. and Palmiter, R.D. Transgenic Mice Harboring SV40 T-Antigen Genes Develop Characteristic Brain Tumors. Cell, 37:367-379, 1984. (CA 38635)

Brodeur, G.M., Seeger, R.C., Schwab, M., Varmus, H.E. and Bishop, J.M. Amplification of N-myc in Untreated Human Neuroblastomas Correlates with Advanced Disease Stage. Science, 224:1121-1124, 1984.

Carswell, E.A., Old, L.J., Kassel, R.L., Green, S., Fiore, N. and Williamson, B., Proc. Natl. Acad. Sci., USA, 72:3666-3670, 1975.

Cavanaugh, A.H., Lawther, R.P., Gokal, P.K. and Thompson, E.A. Glucocorticoid Inhibition of Initiation of Transcription of the DNA Encoding rRNA (rDNA) in Lymphosarcoma P1798 Cells. Proc. Natl. Acad. Sci. USA, 81:718-721, 1984. (CA 22394)

Cavenee, W.K., Hansen, M.F., Nordenskjold, M., Kock, E., Maumenee, I., Squire, J.A., Phillips, R.A. and Gallie, B.L. Genetic Origin of Mutations Predisposing to Retinoblastoma. Science, 228:501-503, 1985.

Craig, R.W. and Sager, R. Suppression of Tumorigenicity in Hybrids of Normal and Oncogene-Transformed CHEF Cells. Proc. Natl. Acad. Sci., USA, 82:2062-2006, 1985. (CA 28428, CA 22427)

Cwikel, B.J., Barouski-Miller, P.A., Coleman, P.L. and Geleherter, T.D. Dexamethosone Inhibition of an Inhibitor of Plasminogen Activator in HTC Hepatoma Cells. J. Biol. Chem., 259:6847-6851, 1984.

Dalla-Favera, R., Wong-Stoal, F. and Gallo, R.C. onc Gene Amplification in Promyelocytic Leukemia Cell Line HL60 and Primary Leukemic Cells of the Same Patient. Nature, 299:61-63, 1982. (CA 37165)

Dunn, A.R., Metcalf, D., Stanley, E., Grail, D., King, J., Nice, E.C., Burgess, A.W. and Gough, N.M. Biological Characterization of Regulators Encoded by Cloned Hemopoietic Growth Factor Gene Sequences In Growth Factors and Oncogenes. Cold Spring Harbor, 1985, in press. (CA 22556)

Eliyahu, D., Raz, A., Gruss, P., Givol, D. and Oren, M. Participation of p53 Cellular Tumor Antigen in Transformation of Normal Embryonic Cells. Nature, 312:646-649, 1984.

Faramisco, J.R., Clark, R., Wong, G., Arnheim, N., Milley, R. and McCormick, F. Transient Reversion of ras Oncogene-induced Cell Transformation by Antibodies Specific for Amino Acid 12 of ras Protein. Nature, 314:639-642, 1985. (CA 39811)

Faramisco, J.R., Gross, M., Kamata, T., Rosenberg, M. and Sweet, R.W. Microinjection of the Oncogene Form of the Human H-ras (T-24) Protein Results in Rapid Proliferation of Quiescent Cells. Cell, 38:109-117, 1984. (CA 39811)

Fasano, O., Birnbaum, D., Edlund, L., Fogh, J. and Wigler, M. New Human Transforming Genes Detected by a Tumorigenicity Assay. Mol. Cell. Biol., 9:1695-1705, 1984. (CA 39829, CA 33928)

Fearon, E.R., Vogelstein, B. and Feinberg, A.P. Somatic Deletion and Duplication of Genes on Chromosome 11 in Wilms' Tumor. Nature, 309:176-178, 1984. (CA 35150)

Feo, S., ar-Rushdi, A., Huebner, K., Finan, J., Nowell, P.C., Clarkson, B. and Croce, C.M. Suppression of the Normal Mouse c-myc Oncogene in Human Lymphoma Cells. Nature, 313:493-495, 1985. (CA 36521, CA 35150)

Fukuda, M. and Fukuda, M.N. Cell Surface Glycoproteins and Carbohydrate Antigens in Development and Differentiation of Human Erythroid Cells In The Biology of Glycoproteins, Plenum Publishing Corporation, 1984. (CA 33895, CA 34014)

Fukushi, Y., Nudelman, E., Levery, S.B. and Hakomori, S. Novel Fucolipids Accumulating in Human Adenocarcinoma III. A Hybridoma Antibody (FH6) Defining a Human Cancer-Associated Difucoganglioside. J. Biol. Chem., 259:10511-10517, 1984. (CA 20026)

Gahmberg, C., Andersson, L.C., Karki, K.K. and Rodt, H. Surface Glycoprotein Changes During Normal and Malignant Hematopoietic Differentiation. Biochem. Soc. Trans., 12:549-552, 1983. (CA 26294)

Gametchu, B. and Harrison, R.W. Characterization of a Monoclonal Antibody to the Rat Liver Glucocorticoid Receptor. Endocrinology, 114:274-279, 1984. (CA 19907)

Gasson, J.C., Golde, D.W., Kaufman, S.E., Hewick, R.M., Kaufman, R.J., Wong, G.G., Temple, P.A., Leary, A.C., Brown, E.L., Orr, E.C. and Clark, S.C. Molecular Characterization and Expression of the Gene Encoding Human Erythroid-Potentiating Activity. Nature, 315:768-771, 1985) (CA 32737, CA 30388)

Gasson, J.C., Weisbart, R.H., Kaufman, S.E., Clark, S.C., Hewick, R.M., Wong, G.G. and Golde, D.W. Purified Human Granulocyte-Macrophage Colony-Stimulating Factor: Direct Action on Neutrophils. Science, 226:1339-1342, 1984. (CA32737, CA 30388)

George, D.L., Scott, A.F., de Martinville, B. and Francke, U. Amplified DNA in Yl Mouse Adrenal Tumor Cells: Isolation of cDNAs Complementary to an Amplified c-Ki-ras gene and Localization of Homologous Sequences to Mouse Chromosome 6. Nuclic Acid Res., 12:2731-2743, 1984. (CA 34462)

Gonda, T.J. and Metcalf, D. Expression of myb, myc and fos Proto-oncogenes During the Differentiation of Murine Myeloid Leukemia. Nature, 310:249-251, 1984. (CA 25972)

Goueli, S.A., Holtzman, J.L. and Ahmed, K. Phosphorylation of the Androgen Receptor by a Nuclear cAMP-independent Protein Kinase. Biochem. Biophys. Res. Comm., 123:778-784, 1984. (CA 15062)

Goustin, A.S. et al. Coexpression of the sis and myc Proto-oncogenes in Developing Human Placenta Suggests Autocrine Control of Trophoblast Growth. Cell 41:301-312, 1985.

Groopman, J.E., Lusis, A.J., Weisbart, R.H., Griffin, F.M. Jr. and Golde, D.W. Human Lymphokines: Insights Gained from Characterization of Products from a T-Lymphocyte Cell Line. Leukemia Reviews International, 2:125-150, 1984. (CA 32737)

Hakomori, S. and Kannagi, R. Glycosphingolipids as Tumor-Associated and Differentiation Markers. J. Natl. Can. Inst., 71:231-251, 1983. (CA 20026, CA 19224, CA 23907)

Hanahan, D. Heritable Formation of Pancreatic B-cell Tumors in Transgenic Mice Expressing Recombinant Insulin/simian Virus 40 Oncogenes. Nature, 315:115-122, 1985.

Howard, S.C., Hull, S.R., Huggins, J.W., Carraway, C.A.C. and Carraway, K.L. Relationship between Xenotransplantability and Cell Surface Properties of Ascites Sublines of a Rat Mammary Carcinoma. J. Natl. Can. Inst., 69:33-40, 1982.

Hurley, J.B., Simon, M.I., Teplow, D.B., Robishaw, J. and Gilman, A.G. Homologies Between Signal Transducing G Proteins and ras Gene Products. Science, 226:860-862, 1984.

Jenkins, J.R., Rudge, K. and Currie, G.A. Cellular Immortalization by a cDNA Clone Encoding the Transformation-associated Phosphoprotein p53. Nature 312: 651-653, 1984.

Kasid, A., Lippman, M.E., Papageorge, A.G., Lowy, D.R. and Gelmann, E.P. Transfection of v-ras H DNA into MCF-7 Human Breast Cancer Cells Bypasses Dependence on Estrogen for Tumorigenicity. Science, 228:725-728, 1985.

Kataoka, T., Powers, S., Cameron, S., Fasano, O., Goldforb, M., Broach, J. and Wigler, M. Functional Homology of Mammalian and Yeast ras Genes. Cell, 40:19-26, 1985. (CA 29569, CA 39829)

Kataoka, T., Powers, S., McGill, C., Fasano, O., Strathern, J., Broach, J. and Wigler, M. Genetic Analysis of Yeast ras 1 and ras 2 Genes. Cell, 37:437-445, 1984. (CA 29569, 39829)

King, R.J.B. Enlightment and Confusion Over Steroid Hormone Receptors. Nature, 312:701-702, 1984.

King, W.J. and Greene, G.L. Monoclonal Antibodies Localize Oestrogen Receptor in the Nuclei of Target Cells. Nature, 307:745-747, 1984.

Klinger, H.P. and Shows, T.B. Suppression of Tumorigenicity in Somatic Cell Hybrids II. Human Chromosomes Implicated as Suppressors of Tumorigenicity in Hybrids with Chinese Ovary Cells. J. Natl. Can. Inst., 71:559-569, 1983. (CA 16720)

Kohl, N.E., Gee, C.E. and Alt, F.W. Activated Expression of the N-myc Gene in Human Neuroblastomas and Related Tumors. Science, 226:1335-1337, 1984.

Koufos, A., Hansen, M.F., Lampkin, B.C., Workman, M.L., Copeland, N.G., Jenkins, N.A. and Cavanee, W.K. Loss of Alleles at Loci on Human Chromosome 11 During Genesis of Wilms' Tumor. Nature, 309:170-172, 1984.

Lachman, H.M and Skoultchi, A.I. Expression of c-myc Changes During Differentiation of Mouse Erythroleukemia Cells. Nature, 310:592-594, 1984. (CA 16368)

Lee, W.H., Murphree, A.L. and Benedict, W.F. Expression and Amplification of N-myc Gene in Primary Retinoblastoma. Nature, 309:458-460, 1984.

Libermann, T.A., Nusbaum, H.R., Razon, N., Kris, R., Lax, I., Soreq, H., Whittle, N., Waterfield, M.D., Ullrich, A. and Schlessinger, J. Amplification, Enhanced Expression and Possible Rearrangement of EGF Receptor Gene in Primary Human Brain Tumours of Glial Origin. Nature, 313:144-147, 1985. (CA 25820)

Liboi, E., Carriso, M. and Basilico, C. New Rat Cell Line that is Highly Susceptible to Transformation by Several Oncogenes. Mol. Cell. Biol., 12:2925-2928, 1984.

Little, C.D., Nau, M.M., Carney, D.N., Gazdar, A.F., Minna, J.D. Amplification and Expression of the c-myc Oncogene in Human Lung Cancer Cell Lines. Nature, 306:194-196, 1983.

Manne, V., Bekesi, E. and Kung, H-F. Ha-ras Proteins Exhibit GTPase Activity: Point Mutations that Activate Ha-ras Gene Products Result in Decreased GTPase Activity. Proc. Natl. Acad. Sci., USA, 82:376-380, 1985.

McGrath, J.P., Capon, D.J., Goeddel, D.V. and Levinson, A.D. Comparative Biochemical Properties of Normal and Activated Human ras p21 Protein. Nature, 310: 644-649, 1984.

Meisfeld, R., Okret, S., Wikstrom, A-C., Wrange, O., Gustafsson, J-A., and Yamamoto, K.R. Characterication of a Steroid Hormone Receptor Gene and mRNA in Wild-type and Mutant Cells. Nature, 312:779-781, 1984. (CA 20535)

Mitchell, R.L., Zokas, L., Schreiber, R.D. and Verma, I.M. Rapid Induction of the Expression of Proto-oncogene fos During Human Monocytic Differentiation. Cell, 40:209-217, 1985.

Mowat, M., Cheng, A., Kimura, N., Bernstein, A. and Benchimol, S. Rearrangements of Cellular p53 gene in Erythroleukaemic Cells Transformed by Friend Virus. Nature, 314:633-636, 1985.

Mulcahy, L.S., Smith, M.R., Stacey, D.W. Requirement for ras Proto-oncogene Function During Serum-Stimulated Growth of NIH 3T3 Cells. Nature, 313:241-243, 1985.

Muller, R., Curran, T., Muller, D., and Guilbert, L. Inducation of c-fos During Myelomonocytic Differentiation and Macrophage Proliferation. Nature, 314:546-548, 1985.

Munck, A. and Crabtree, G.R. Glucocorticoid-induced Lymphocyte Death, In Cell Death in Biology and Pathology, Chapman and Hall, London and New York, pp. 329-359, 1981. (CA 17323)

Murphree, A.L. and Benedict, W.F. Retinoblastoma: Clues to Human Oncogenesis. Science, 223:1028-1034, 1984.

Nakano, H., Yamamoto, F., Neville, C., Evans, D., Mizuno, T. and Perucho, M. Isolation of Transforming Sequences of Two Human Lung Carcinomas: Structural and Functional Analysis of the Activated c-K-ras Oncogenes. Proc. Natl. Acad. Sci., USA, 81:71-75, 1984. (CA 33021)

Nicole, N.A. and Metcalf, D. Binding of the Differentiation-Inducer, Granulocyte-Colony-Stimulating Factor, to Responsive but not Unresponsive Leukemic Cell Lines. Proc. Natl. Acad. Sci., USA, 81:3765-3769, 1984. (CA 22556)

Orkin, S.H., Goldman, D.S. and Sallan, S.E. Development of Homozygosity for Chromosome 11p Markers in Wilms' Tumour. Nature, 309:172-174, 1984.

Parada, L.F., Land, H., Weinberg, R.A., Wolf, D. and Rotter, V. Cooperation Between Gene Encoding p53 Tumor Antigen and ras in Cellular Transformation. Nature, 312:649-651, 1984. (CA 40002)

Pellicci, P-G., Lanfrancone, L., Brathwaite, M.D., Wolman, S.R. and Dalla-Favera, R. Amplification of the c-myb Oncogene in a Case of Human Acute Myelogeous Leukemia. Science, 224:1119-1121, 1984. (CA 37165)

Pennica, D., Nedwin, G.E., Hayflick, J.S., Seeburg, P.H., Derynck, R., Palladino, M.A., Kohr, W.J., Aggarwal, B.B. and Goeddel, D.V. Human Tumour Necrosis Factor: Precursor Structure, Expression and Homology to Lymphotoxin. Nature, 312:724-728, 1984.

Pfeifer-Ohlsson, S., Goustin, A.S., Rydnert, J., Wahlstrom, T., Bjersing, L., Stehelin, D. and Ohlsson, R. Spatial and Temporal Pattern of myc Oncogene Expression in Developing Human Placenta: Implication for Embryonic Cell Proliferation. Cell, 38: 585-596, 1984.

Pratt, T. and Sherblom, A.P. Sialyltransferase of the 13762 Rat Mammary Ascites Tumor Cells. Cancer Res., 44:1148-1152, 1984. (CA 33238)

Propst, F. and Vande Woude, G.F. Expression of c-mos Proto-oncogene Transcripts in Mouse Tissues. Nature, 315:516-518, 1985.

Reeve, A.E., Housiaux, P.J., Gardner, R.J.M., Chewings, W.E., Grindley, R.M. and Mellow, L.J. Loss of a Harvey ras Allele in Sporadic Wilms' Tumour. Nature, 309:174-176, 1984.

Reich, N.C. and Levine, A.J. Growth Regulation of a Cellular Tumor Antigen, p53, in Non-Transformed Cells. Nature, 308:199-201, 1984. (CA 38964)

Rettenmier, C.W., Roussel, M.F., Quinn, C.O., Kitchingman, G.R., Look, A.T. and Sherr, C.J. Transmembrane Orientation of Glycoproteins Encoded by the v-fms Oncogene. Cell, 40:971-981, 1985.

Rettenmier, C.W., Chen, J.H., Roussel, M.F. and Sherr, C.J. The Product of the c-fms Proto-oncogene: A Glycoprotein with Associated Tyrosine Kinase Activity. Science, 228:320-322, 1985

Robertson, M. Message of myc in Context. Nature, 309:585-587, 1984.

Roninson, I.B., Abelson, H.T., Housman, D.E., Howell, N. and Varshavsky, A. Amplification of DNA Sequences Correlates with Multi-Drug Resistance in Chinese Hamster Cells. Nature, 309:626-628, 1984. (CA 39365)

Roussel, M.F., Rettenmier, C.W., Lock, A.T. and Sherr, C.J. Cell Surface Expression of v-fms-Coded Glycoproteins is Required for Transformation. Mol. Cell. Biol., 4:1999-2009, 1984.

Santer, U.V., Gilbert, F. and Glick, M.C. Change in Glycosylation of Membrane Glycoproteins after Transfection of NIH 3T3 with Human Tumor DNA. Cancer Res., 44:3730-3735, 1984. (CA 37853, CA 36122)

Schimke, R.T. Gene Amplification in Cultured Animal Cells. Cell, 37:705-713, 1984.

Schrader, W.T. New Model for Steroid Hormone Receptors ?, Nature, 308:17-18, 1984

Schwab, M., Alitalo, K., Klempnauer, K-H., Varmus, H.E., Bishop, J.M., Gilbert, F., Brodeur, G., Goldstein, M. and Trent, J. Amplified DNA with Limited Homology to myc Cellular Oncogene is Shared by Human Neuroblastoma Cell Lines and Neuroblastoma Tumour. Nature, 305:245-248, 1983. (CA 29476)

Schwab, M., Ellison, J., Busch, M., Rosenau, W., Varmus, H.E. and Bishop, J.M. Enhanced Expression of the Human Gene N-myc Consequent to Amplification of DNA May Contribute to Malignant Progression of Neuroblastoma. Proc. Natl. Acad. Sci., USA., 81:4940-4944, 1984.

Schwab, M., Ramsay, G., Alitalo, K., Varmus, H.E., Bishop, J.M., Martinsson, T., Levan, G. and Levan, A. Amplification and Enhanced Expression of the c-myc Oncogene in Mouse SEWA Tumour Cells. Nature, 315:345-347, 1985.

Sherman, M.R. and Stevens, J. Structure of Mammalian Steroid Receptors: Evolving Concepts and Methodological Developments. Ann. Rev. Physiol., 46:83-105, 1984. (CA 32178)

Sherr, C.J., Rettenmier, C.W., Sacca, R., Roussel, M.F., Look, A.T. and Stanley, E.R. The c-fms Proto-oncogene Product is Related to the Receptor for Mononuclear Phagocyte Growth Factor, CSF-1. unpublished, 1985.

Shikuya, M., Tokota, J. and Ueyama, Y. Amplification and Expression of a Cellular Oncogene (c-myc) in Human Gastric Adenocarcinoma Cells. Mol. Cell. Biol., 5:414-418, 1985.

Slamon, D.J. and Cline, M.J. Expression of Cellular Oncogenes During Embryonic and Fetal Development of the Mouse. Proc. Natl. Acad. Sci., USA, 81:7141-7145, 1984. (CA 36827)

Solomon, E. Recessive Mutation in Aetiology of Wilms' Tumour. Nature, 309: 111-112, 1984.

Spandidos, D.A. and Wilkie, N.M. Malignant Transformation of Early Passage Rodent Cells by a Single Mutated Human Oncogene. Nature, 310:469-475, 1984.

Stacey, D.W. and Kung, H-F. Transformation of NIH 3T3 Cells by Microinjection of Ha-ras p21 Protein. Nature, 310:508-511, 1984.

Stanbridge, E.J., Fagg, B. and Der, C.J. Differentiation and Control of Tumorigenicity In Human Cell Hybrids In Human Carcinogenesis. Academic Press, Inc., pp. 97-122, 1983. (CA 19401)

Stanbridge, E.J. Genetic-Analysis of Tumorigenicity in Human Cell Hybrids. Cancer Surveys, 3, 1984. (CA 19401)

Stanley, E.R. Colony-stimulating Factor (CSF) Radioimmunoassay: Detection of a CSF Subclass Stimulating Macrophage Production. Proc. Natl. Acad. Sci., USA, 76:2969-2971, 1979.

Stanley, P. Membrane Mutants of Animal Cells: Rapid Identification of those with a Primary Defect in Glycosylation. Mol. Cell. Biol., 5:923-929, 1985. (CA 30645, CA 36434)

Stewart, T.A., Pattengale, P.K. and Leder, P. Spontaneous Mammary Adenocarcinomas in Transgenic Mice that Carry and Express MTV/myc Fusion Genes. Cell, 38:627-637, 1984.

Stoler, A. and Bouck, N. Identification of a Single Chromosome in the Normal Human Genome Essential for Suppression of Hamster Cell Transformation. Proc. Natl. Acad. Sci., USA. 82:570-574, 1984.

Sweet, R.W., Yokoyama, S., Kamata, T., Faramisco, J.R., Rosenberg, M. and Gross, M. The Product of ras is a GTPase and the T24 Oncogenic Mutant is Deficient in this Activity. Nature, 311:273-275, 1984. (CA 39811)

Temeles, G.L., Gibbs, J.B., D'Alonzo, J.S., Sigal, I.S. and Scolnik, E.M. Yeast and Mammalian ras Proteins Have Conserved Biochemical Properties. Nature, 313:700-703, 1985.

Thompson, E.B., Zawydiwski, R, Brower, S.T., Eisen, H.J., Simons, S.S. Jr., Schmidt, T.J., Schlechte, J.A., Moore, D.E., Norman, M.R. and Harmon, J.M. Properties and Function of Human Glucocorticoid Receptors in Steroid-Sensitive and-resistant Leukemic Cells, In Steroid Hormone Receptors: Structure and Function, Elsevier Science Publishers, 1983, pp. 171-194. (CA32226)

Thorgeirsson, U.P., Hujanen-Turpeenniemi, T., Williams, J.E., Westin, E.H., Heilman, C.A., Talmadge, J.E. and Liotta, L.A. NIH 3T3 Cells Transfected with Human Tumor DNA Containing Activated ras Oncogenes Express the Metastatic Phenotype in Nude Mice. Mol. Cell. Biol., 5:259-262, 1985.

Toda, T., Uno, I., Ishikawa, T., Powers, S., Kataoka, T., Broek, D., Cameron, S., Broach, J., Matsumoto, K. and Wigler, M. In Yeast ras Proteins are Controlling Elements of Adenyl Cyclase. Cell 40:27-36, 1985. (CA 29569, CA 39829)

Ullrich, A., Coussens, L., Hayflick, J.S., Dull, T.J., Gray, A., Tam, A.W., Yarden, Y., Lee, J., Liebermann, T.A., Schlessinger, J., Downward, J., Mayes, E.L.V., Whittle, N., Waterfield, M.D. and Seeburg, P.H. Human Epidermal Growth Factor Receptor cDNA Sequence and Aberrant Expression of the Amplified Gene in A431 Epidermoid Carcinoma Cells. Nature, 309:418-425, 1984. (CA 25820)

Wang, A.M., Creasey, A.A., Ladner, M.B., Lin, L.S., Strickler, J., Van Arsdell, J.N., Yamamoto, R. and Mark, D.F. Molecular Cloning of the Complementary DNA for Human Tumor Necrosis Factor. Science, 228:149-154, 1985.

Warren, L., Baker, S.R., Blith, D.L. and Buck, C.A. The Role of Carbohydrates Bound to Proteins In Biomembranes, Plenum Publishing Corporation, 1983. (CA 19130)

Warren, L. and Cossu, G. The Bound Carbohydrates of Glycoproteins in Normal and Pathological States In Endothelium. N.Y. Academy of Sciences, 401:85-91, 1983a. (CA 19130)

Warren, L. and Cossu, G. Altered Glycoprotein Carbohydrates in Malignant Cells. Gann Monograph on Cancer Research, 29:107-111, 1983b. (CA 19130)

Weinberger, C., Hollenberg, S.M., Ong. E.S., Harmon, J.M., Brower, S.T., Cidlowski, J., Thompson, E.B., Rosenfeld, M.G. and Evans, R.M. Identification of Human Glucocorticoid Receptor Complementary DNA Clones by Epitope Selection. Science, 228:740-742, 1985. (CA 32226)

Welshons, W.V., Lieberman, M.E. and Gorski, J. Nuclear Localization of Unoccupied Oestrogen Receptors, Nature, 307:747-749, 1984. (CA 18110)

Wolf, D., Harris, N. and Rotter, V. Reconstitution of p53 Expression in a Nonproducer Ab-MuLV- Transformed Cell Line by Transfection of a Functional p53 Gene. Cell, 38:119-226, 1984. (CA40002)

Wong, G.G. et al. Human GM-CSF: Molecular Cloning of the Complementary DNA and Purification of the Natural and Recombinant Proteins. Science, 228:810-815, 1985. (CA 32737, CA 30388)

Wood, K.M. and Thompson, E.A. Isolation and Characterization of Lymphosarcoma P1798 Variants Selected for Resistance to the Cytolytic Effects of Glucocorticoids in vivo and Culture. Mol. Cell. Endo., 37:169-180, 1984. (CA 24347, CA 22394)

Yamamoto, K.R. Steroid Receptor Regulated Transcription of Specific Genes and Gene Networks. Ann. Rev. Genetics, 19, in press, 1985. (CA 20535)

Yoakum, G.H. et al. Transformation of Human Bronchial Epithelial Cells Transfected by Harvey ras Oncogene. Science, 227:1174-1179, 1985.

Zarkle, H., Sukumar, S., Arthur, A.V., Martin-Zanca, D. and Barbacid, M. Direct Mutagenesis of Ha-ras-1 Oncogenes by N-nitroso-N-methylurea During Initiation of Mammary Carcinogenesis in Rats. Nature, 315:382-385, 1985.

FISCAL YEAR 1985 EST.

TUMOR BIOLOGY PROGRAM
SUMMARY BY SUB CATEGORY (DOLLARS IN THOUSANDS)

		NON-COMPETING		COMPETING		TOTAL	
		No.	Amount	No.	Amount	No.	Amount
A.	Cell Surface	56	$7,523	24	$3,584	80	$11,107
B.	Enzymes	28	3,621	8	1,050	36	4,671
C.	Peptide Hormones	16	2,127	3	414	19	2,541
D.	Steroids	15	2,161	10	1,495	25	3,656
E.	Membraneous Organelles	5	727	4	963	9	1,690
F.	Ribosomes & Polyribosomes	4	789	0	0	4	789
G.	M-RNA	9	1,477	5	726	14	2,203
H.	T-RNA	6	606	0	0	6	606
I.	DNA	11	1,526	2	271	13	1,797
J.	Growth Factors	31	4,193	16	1,884	47	6,077
K.	Nucleus	11	1,059	3	292	14	1,351
L.	Contractile Elements	9	1,074	8	868	17	1,727
M.	Development & Differentiation	49	6,507	12	1,779	61	8,286
N.	Cell Growth, Cell Division	23	2,819	5	721	28	3,540
O.	Metastasis	0	0	3	354	3	354
P.	Somatic Cell Genetics	5	786	4	575	9	1,361
Q.	Inheritance of Neoplasms	0	0	1	133	1	133
R.	Plasmids, Viruses	0	0	1	189	1	189
S.	In Vivo & In Vitro Tumor Lines	5	450	2	298	7	748
W.	Difficult to Classify	1	367	4	602	5	969
X.	Oncogenes	13	1,803	23	3,339	36	5,142
	SUB TOTAL	297	39,615	138	19,537	435	59,152
V.	Program Projects	14	12,792	0	0	14	12,792
U.	Small Business Grants	1	222	2	98	3	320
T.	Conferences	1	23	10	57	11	80
Y.	Outstanding Investigators	0	0	5	1,068	5	1,068
	SUB TOTAL	16	13,037	17	1,223	33	14,260
	TOTAL	313	$52,652	155	$20,760	468	$73,412

R01 CA08759 Structure, Biosynthesis and Function of Glycoproteins
Kornfeld Washington University

R01 CA12306 Role of Cell Surface in Initiation of Cell Division
Cunningham University of California, Irvine

R01 CA12790 Membrane Transport Adaptations by Human Lymphocytes
Lichtman University of Rochester

R01 CA13402 Surface Membranes in Normal and Cancer Cells
Atkinson Yeshiva University

R01 CA13605 Chemistry and Measurement of Intercellular Adhesion
Steinberg Princeton University

R01 CA14464 Intercellular Communication and Cancer
Loewenstein University of Miami

R01 CA14551 Penetration of Macromolecules into Mammalian Cells
Ryser Boston University

R01 CA14609 Molecular Basis of Cellular Adhesiveness
Grinnell University of Texas Health Science Center, Dallas

R01 CA14764 Glycolipid Metabolism in Tumor and Transformed Cells
Basu University of Notre Dame

R01 CA15047 O-Alkyl Lipids in Surface Membranes of Tumor Cells
Friedberg University of Texas Health Science Ctr., San Antonio

R01 CA15483 Biochemistry of Mucopolysaccharides
Davidson Pennsylvania State University Hershey Medical Center

R01 CA16740 Proteases in Growth Control and Malignant Transformation
Quigley Downstate Medical Center

R01 CA16777 The Biosynthesis of Cell Envelope Glycoproteins
Schutzbach University of Alabama in Birmingham

R01 CA17007 Cell Surface Structure and Cell Transformations
Hynes Massachusetts Institute of Technology

R01 CA18470 Antigenicity and Tumorigenicity of Somatic Cell Hybrids
Knowles Wistar Institute of Anatomy and Biology

R01 CA18801 Glycolipid Metabolism and Tumorigenesis
Morre Purdue University, West Lafayette

R01 CA19144 Membrane Changes Caused by Tumor Virus Transformation
Buck Wistar Institute of Anatomy and Biology

R01 CA20026 Glycolipids of Normal and Transformed Cells
Hakomori Fred Hutchinson Cancer Research Center

R01 CA20421 Mutants Altered in Glycosylation of Soluble & Membrane Proteins
Krag Johns Hopkins University

R01 CA20424 Murine Ascites Tumor Cell Glycoproteins
Goldstein University of Michigan at Ann Arbor

R01 CA21246 The Roles of Laminin and Entactin in Cell Adhesion
Chung University of Pittsburgh

R01 CA21463 Steroid Correction of the Cell Matrix in Neoplasia
Furcht University of Minnesota of Minneapolis-St. Paul

R01 CA21722 Membrane Pathology in Carcinogenesis
Scott Mayo Foundation

R01 CA21923 Oligosaccharide Structure and Function in Recognition
Baenziger Washington University

R01 CA22202 Studies of Fibrin Deposition in Cancer
Rickles University of Connecticut Health Center

R01 CA22451 Contact Behavior of Developing and Transformed Cells
Trinkaus Yale University

R01 CA22659 Studies of Proteins Involved in Cell Interaction
Chen Dana-Farber Cancer Institute

R01 CA22729 Hormonal Regulation of Membrane Phenotype
Gelehrter University of Michigan at Ann Arbor

R01 CA23540 Collagen and Its Relationship to Tumors
Smith Boston University

R01 CA23753 Proteases and the Malignant Phenotype
Rifkin New York University

R01 CA23907 Fibronectin and Other Glycoproteins Defining Malignancy
Hakomori Fred Hutchinson Cancer Research Center

R01 CA25730 Adhesion and Surface Membrane in Mammary Carcinomas
Steiner University of Kentucky

R01 CA26122 Effects of Hormones on Cell Membrane Properties
Baumann Roswell Park Memorial Institute

R01 CA26294 Glycoproteins of Normal/Malignant Human Blood Cells
Gahmberg University of Helsinki

R01 CA27117 A Study of Membrane Bound ATPases of Human Tumor
Knowles University of California, San Diego

R01 CA27460 Alpha-Fetoprotein: Structure and Function
Ruoslahti La Jolla Cancer Research Foundation

R01 CA27648 Tumorigenesis and a Cell Surface Growth Inhibitor
Johnson Kansas State University

R01 CA27755 Fibronectin: Proteoglycan Binding in Adhesion Sites
Culp Case Western Reserve University

R01 CA28287 Driving Forces for Nutrient Transport in Tumor Cells
Smith University of Texas Health Science Center, San Antonio

R01 CA28471 Biology of Solid Tumor Growth and Immune Rejection
Dvorak Beth Israel Hospital

R01 CA28548 Developing Immunological Probes for Gap Junctions
Johnson University of Minnesota

R01 CA29571 Malignant Cell Variants of Lymphosarcoma
Nicolson University of Texas System Cancer Center

R01 CA29995 Role of Laminin in Metastasis and Migration of Tumor Cells
Furcht University of Minnesota of Minneapolis-St. Paul

R01 CA30117 Regulation of Cells by Matrix and Hormones
Reid Yeshiva University

R01 CA30289 Epithelial Cells--Extracellular Matrix Interactions
Vlodavsky Hadassah University Hospital

R01 CA30645 Glycosylation Mutants of Animal Cells
Stanley Yeshiva University

R01 CA31103 Molecular Determinants of Multicellular Organization
Hixson University of Texas System Cancer Center

R01 CA31277 Galactosyltransferase in Malignancy and Transformation
Isselbacher Massachusetts General Hospital

R01 CA32311 Cytoskeleton-Membrane Interaction--Antisera Induced CHA
Damsky Wistar Institute of Anatomy and Biology

R01 CA32927 Anion Transport in Ehrlich Carcinoma Cells
Levinson University of Texas Health Science Center, San Antonio

R01 CA32949 Biosynthesis and Secretion of HCG by Human Trophoblasts
Ruddon University of Michigan at Ann Arbor

R01 CA33074 Cell Adhesion Proteins and Malignancy
Klebe University of Texas Health Science Center, San Antonio

R01 CA33208 Prostate Cell Surface Phenotype and Tumor Behavior
Ware Duke University

R01 CA33238 Sialylation of a Tumor Cell Glycoprotein
Sherblom University of Maine at Orono

R01 CA33362 Mechanisms of Nucleoside Transport in Mammalian Cells
Belt St. Jude Children's Research Hospital

R23 CA33751 II-Glycolipid Biosynthesis in Lymphomas
Basu University of Notre Dame

R01 CA33834 Tumor Cell Invasion of Microvessel Subendothelial Matrix
Kramer University of California, San Francisco

R01 CA34014 Endo-Beta Galactosidase and Cell Surface Glycoconjugate
Fukuda La Jolla Cancer Research Foundation

R01 CA34691 A Specific Abnormality in Chronic Leukemic Lymphocytes
Segel University of Rochester

R01 CA34918 Structure of Carbohydrate Moieties of Glycoproteins
Olden Howard University

R01 CA35377 Complex Asparagine-Linked Carbohydrates
Pierce University of Miami

R01 CA36069 Cell Contact in Regulation of Embryonal Carcinoma
Wells University of Colorado Health Sciences Center

R01 CA36132 Endogenous Laminin Expression and Metastasis
Varani University of Michigan at Ann Arbor

R01 CA36248 Granulocyte Membrane Structure and Function
Skubitz University of Minnesota of Minneapolis-St. Paul

R01 CA36434 Glycosylation Defects of Lectin-Resistant Tumor Cells
Stanley Yeshiva University

R23 CA37191 Molecular Heterogeneity of Fibronectins
Sekiguchi Fred Hutchinson Cancer Research Center

R01 CA37626 Surface Oligosaccharides in Embryonal Carcinoma Cells
Cummings University of Georgia

R01 CA37662 Substrate-Specific Adhesive Variants of Metastatic Cells
Briles University of Texas System Cancer Center

R01 CA37785 Regulation of Fibronectin Matrix Assembly
McKeown-Longo State University of New York at Albany

R01 CA37853 Structures of Neurectoderm Tumor Glycoproteins
Glick Children's Hospital of Philadelphia

R23 CA38006 New Focal Contact Proteins and Transformation
Maher University of California, San Diego

R01 CA38701 Sulfated Oligosaccharides of Normal and Malignant Cells
Varki University of California

R01 CA38773 Proteins of the Hepatoma Cell Plasma Membrane
Doyle State University of New York at Buffalo

R01 CA38801 Structure and Function of the Carbohydrate Units of GP140
Carter Pacific Northwest Research Foundation

R01 CA38817 Fibroblast Tumor Cell Interactions in Tumor Invasion
Biswas Tufts University

R01 CA38849 Pteridine Metabolism and Transport in Malignant Cells
Webber Scripps Clinic and Research Foundation

R01 CA39037 Basement Membranes of Cultured Cells - A Model System
Keller University of Health Sciences/Chicago Medical School

R01 CA39077 Molecular Ultrastructure Underlying Cell Adhesion
Chen Georgetown University

R01 CA39422 Role of Tumor Cell Surface Lectins in Metastasis
Lotan University of Texas System Cancer Center

R01 CA39604 Cell Interactions During Malignant Transformation
Bertram University of Hawaii at Manoa

R01 CA39919 Analysis of Extracellular Matrix of Transforming Cells
Hawkes University of California, San Francisco

R23 CA39982 Metastasis of Human Lung Adenocarcinoma
Varki University of California, Los Angeles

R01 CA40059 Extracellular Components in Blood Stromal Cell Interaction
Sorrell West Virginia University

R01 CA40225 The Desmoplastic Response to Tumor Invasion
Barsky University of California

R01 CA40422 Basement Membrane Degradation by Tumor Cells
Jones University of Southern California

R01 CA40475 Cell-Substratum Interactions
Barnes Oregon State University

R01 CA40624 Pathogenesis of Tumor Stroma Generation
Dvorak Beth Israel Hospital

R01 CA41220 Gene Amplification in Carcinogenesis
Miller Wayne State University

R01 CA04679 Biology of Normal and Malignant Melanocytes
Lerner Yale University

R01 CA10916 Metabolism of Normal and Neoplastic Tissue
Weinhouse Temple University

R01 CA11655 Studies of Leukocyte Metabolism
Silber New York University

R01 CA14881 Regulation of Tyrosine Synthesis in Hepatoma Cells
Shiman Pennsylvania State University Hershey Medical Center

R01 CA15979 Cholesterol Metabolism in Normal and Malignant Liver
Siperstein University of California, San Francisco

R01 CA18138 Mammalian Polyamine Metabolism
Pegg Pennsylvania State University Hershey Medical Center

R01 CA22717 Regulation of Folate Poly-Gamma-Glutamate Synthesis
Shane Johns Hopkins University

R01 CA25005 The Regulation of Mammalian Enzyme Synthesis
Greengard Mount Sinai School of Medicine

R01 CA25617 The Collagenolytic System of Invasive Tumors
Dabbous University of Tennessee Center Health Sciences

R01 CA26546 The Regulation of Polyamine Biosynthesis
Canellakis Yale University

R01 CA27674 Control of Pyrimidine Biosynthesis in Mammalian Cells
Evans Wayne State University

R01 CA27808 Neuroendocrine Gene Expression in Neoplastic Progression
Tischler Tufts University

R01 CA28111 Hormonal Regulation of Kidney Epithelial Cell Growth
Taub State University of New York at Buffalo

R01 CA28376 Nucleotide Metabolism in Chronic Lymphocytic Leukemia
Silber New York University

R01 CA28725 Asparagine Biosynthesis in Normal and Tumor Cells
Schuster University of Nebraska, Lincoln

R01 CA28781 Biosynthesis of Dolichyl Phosphate
Adair University of South Florida

R01 CA29048 Mechanisms of Ornithine Decarboxylase Regulation
Coffino University of California, San Francisco

R01 CA29307 Control of Protease Action on Human Cells
Baker University of Kansas, Lawrence

R01 CA29331 Regulation of Cystathionase Expression
Glode University of Colorado Health Sciences Center

R01 CA32022 Characterization of a Novel Lactate Dehydrogenase
Anderson Roswell Park Memorial Institute

R01 CA32369 Folate Binders in Hematopoiesis and Cell Replication
Da Costa Downstate Medical Center

R01 CA32941 Role of Plasminogen Activator in Cell Transformation
Kacian University of Pennsylvania

R23 CA33732 Metabolism of N-13 Ammonia and L-Amino Acids in Tumors
Rosenspire Sloan-Kettering Institute for Cancer Research

R23 CA34025 Secreted Phosphoproteins Associated with Tumorigenicity
Senger Beth Israel Hospital, Boston

R01 CA34517 Mechanism of Transformation by Tyrosine Kinases
Clinton Louisiana State University Medical Center, New Orleans

R01 CA34746 Inhibitors of Tyrosine-Specific Protein Kinase
Tam Rockefeller University

R01 CA35680 Maturation of Human Myeloid Leukemia
Niedel Duke University

R01 CA36481 Cathepsin B-Like Cysteine Proteinases and Tumor Invasion
Sloane Wayne State University

R01 CA36777 Phospholipid-Ca2+ and Phosphoproteins in Leukemic Cells
Kuo Emory University

R01 CA38821 Properties of a Lymphoma Cell Tyrosine Protein Kinase
Casnellie University of Rochester

R01 CA38992 Molecular Analysis of NA^+/K^+-ATPase
Levenson Yale University

R01 CA39232 cAMP Tyrosine Protein Kinases in Reverse Transformation
Lockwood Albert Einstein Medical Center, Phildelphia

R23 CA40495 HMG COA Reductase Regulation in Human Leukemia
Harwood University of Florida

R01 CA40758 Factors Involved in Malignant Behavior of Human Tumors
Ossowski Rockefeller University

R01 CA41973 A New Assay for Transformed Cells
Mangel Associated University-Brookhaven National Laboratory

R01 CA41991 Regulation of Folylpolyglutamate Synthesis
Shane University of California, Berkeley

PEPTIDE HORMONES (C)

R01 CA07535 Control of Pituitary Gland and Pituitary Tumor Hormones
MacLeod University of Virginia, Charlottesville

R01 CA11685 Tumor Cell Synthesis and Secretion of Peptide Hormones
Orth Vanderbilt University

R01 CA16417 Pituitary Hormones in Normal and Neoplastic Growth
Ramachandran University of California, San Francisco

R01 CA22394 Hormonal Control of Cell Proliferation
Thompson University of South Carolina at Columbia

R01 CA23185 Regulation of Alpha and Beta Subunits of TSH
Kourides Sloan-Kettering Institute for Cancer Research

R01 CA23248 Prolactin Cell Function in Breast Cancer
Hymer Pennsylvania State University, University Park

R01 CA23357 HCGB From Cervical Cancer: Peptide Heterogeneity
Hussa Medical College of Wisconsin

R01 CA24604 Triiodothyronine Receptors and Nonthyroidal Diseases
Surks Montefiore Medical Center, Bronx, New York

R01 CA28218 Hormone Production by Pituitary Tumor Cells
Biswas Harvard University

R01 CA30388 Humoral Regulation of Normal and Malignant Hemopoiesis
Golde University of California, Los Angeles

R01 CA33030 Neuroendocrine Peptide Switching Events in Cancer
Rosenfeld University of California, San Diego

R01 CA33320 Cancer-Hypercalcemia: Secreted Bone-Resorbing Factor
Segre Massachusetts General Hospital

R01 CA33852 Secretion and Proliferation in Small Cell Carcinoma
Sorenson Dartmouth College

R01 CA36399 Lineages in Mammary Cell Transformation
McGrath Michigan Cancer Foundation

R01 CA36526 Expression of Human Chorionic Gonadotropin Genes
Kourides Sloan-Kettering Institute for Cancer Research

R01 CA36718 Mechanism of Ectopic Hormone Synthesis by Tumor Cells
Cox University of Nebraska Medical Center

R01 CA37370 Ectopic Hormone Synthesis in Pheochromocytoma Cells
Goodman New England Medical Center Hospital

R01 CA38651 Gastrointestinal Hormones in Gastrointestinal Cancer
Singh University of Texas Medical Branch, Galveston

R01 CA40629 Gonadotropin Actions in Leydig Tumor Cells
Ascoli Population Council

STEROIDS (D)

R01 CA02758 Steroid Metabolism in Tumors and Normal Tissues
Kandutsch Jackson Laboratory

R01 CA08315 Steroid Induced Changes in Cultured Malignant Cells
Melnykovych University of Kansas, College of Health Sci. and Hosp.

R01 CA13410 Mechanism of Hormone Action on Target Cells in Culture
Sonnenschein Tufts University

R01 CA15648 Steroid Dynamics in Human Endometrial Cancer
Gurpide Mount Sinai School of Medicine

R01 CA17323 Glucocorticoid-Resistant Leukemic Lymphocytes
Munck Dartmouth College

R01 CA18110 Prolactin Synthesis in Normal and Neoplastic Tissue
Gorski University of Wisconsin, Madison

R01 CA19907 Physiology of Pituitary Cell Glucocorticoid Binding
Harrison Vanderbilt University

R01 CA20535 Gene Regulation by Steroid Receptor Proteins
Yamamoto University of Calfornia, San Francisco

R01 CA24347 Hormonal Control of Proliferation of Malignant Thymocytes
Thompson University of South Carolina at Columbia

R01 CA25365 Hormonal Regulation of Cultured Endometrial Cells
Gerschenson University of Colorado Health Sciences Center

R01 CA26617 Estrogen Mediated Pituitary Tumor Cell Growth
Sirbasku University of Texas Health Sciences Center, Houston

R01 CA27702 Sex Hormones, Cancer and the Immune System
Siiteri University of California, San Francisco

R01 CA29497 An Adrenal Tumor: Cytochrome P-450 and Steroidogenesis
Hall Worcester Foundation for Experimental Biology

R01 CA29808 Molecular Mechanism of Desensitization
Iyengar Baylor College of Medicine

R01 CA30253 A Study of Tropic Hormone Action in Carcinoma Cells
Mason University of Texas Health Science Center, Dallas

R01 CA31046 Mechanism of Estrogen Action on Melanocyte Function
Beattie University of Illinois at Chicago

R01 CA32226 Steroid Resistance in Human Leukemic Cells
Harmon U.S. Uniformed Services Univ. of Hlth. Sci.

R01 CA32767 Steroid Receptors in Human Gynecologic Carcinoma Cells
Crickard State University of New York at Buffalo

R01 CA34860 Corticosteroids: Cytokinetic and Biochemical Studies
Braunschweiger AMC Cancer Research Center and Hospital

R01 CA36146 Studies of Regulation in E. Coli Extended to Lymphomas
Bourgeois-Cohn Salk Institute for Biological Studies

R01 CA36370 Tumor-Associated DNA Movement
Selsing Brandeis University

R01 CA37676 Glucocorticoid Receptor Defects in Human Leukemia Cells
Distelhorst Washington University

R23 CA38327 Tumor-Associated Renal Phosphate Wasting
Adams University of Connecticut Health Center

R01 CA38769 Glucocorticoid Receptors in Childhood Leukemia
Costlow St. Jude Children's Research Hospital

R01 CA39657 Hormonal Control of GCDFP-15 Secretion In Vitro
Dilley Washington University

R01 CA40104 Role of Stroma in Mammary Gland Cell Proliferation
Haslam Michigan State University

MEMBRANEOUS ORGANELLES (E)

R01 CA06576 Biochemical Cytology of Normal and Malignant Tissues
Novikoff Yeshiva University

R01 CA08964 Energy Metabolism in Normal and Tumor Cells
Racker Cornell University, Ithaca

R01 CA10951 Control of Enzymatic Phosphate Transfer in Mitochondria
Pedersen Johns Hopkins University

R01 CA12858 Lysosome Biogenesis: Normal and Tumor Cells
Stahl Washington University

R01 CA27809 Pathways of Energy Metabolism in Malignancy In Vitro
Sauer Mary Imogene Bassett Hospital

R01 CA28677 Transport in Cholesterol-Rich Tumor Mitochondria
Coleman New York University

R01 CA32742 Glucose Catabolism in Neoplastic Tissues
Pedersen Johns Hopkins University

R01 CA32946 Transport-Regulated Calcium Metabolism in Tumor Cells
Fiskum George Washington University

R01 CA37197 Lysosomes in Growth Control of Human Neoplastic Cells
Polet University of Illinois at Chicago

R01 CA38891 Integration of Metabolic Pathways in Tumor Mitochondria
Lehninger Johns Hopkins University

RIBOSOMES AND POLYRIBOSOMES (F)

R01 CA04186 Molecular Structure of Nucleic Acids and Proteins
Rich Massachusetts Institute of Technology

R01 CA08416 Form and Function of Nuclear and Cytoskeletons
Penman Massachusetts Institute of Technology

R01 CA16608 Translation Control in Reticulocytes and Leukemic Cells
Hardesty University of Texas, Austin

R01 CA21663 Intermediary Metabolism in Animals and in Man
Henshaw University of Rochester

M-RNA (G)

R01 CA12550 RNA Synthesis and Transport in Mammalian Cells
Martin University of Chicago

R01 CA16006 RNA and Growth Control in Animal Cells
Darnell Rockefeller University

R01 CA20124 Messenger RNA of Normal and Malignant Human Cells
Saunders University of Texas System Cancer Center

R01 CA23226 Gene Expression in Regenerating and Neoplastic Livers
Fausto Brown University

R01 CA25078 Poly(A) Polymerase and mRNA Processing
Jacob Pennsylvania State University Hershey Medical Center

R01 CA27607 Coordinated Gene Expression in Mammaliam Cells
Lee University of Southern California

R01 CA31810 Control of mRNA Processing in Normal and Transformed Cells
Rottman Case Western Reserve University

R01 CA31894 Control of RNA Synthesis by Carcinogens and Hormones
Jacob Pennsylvania State University Hershey Medical Center

R01 CA33643 Mechanisms of Regulation of Cell Proliferation
Getz Mayo Foundation

R01 CA33953 mRNA Turnover in Differentiating Leukemia Cells
Volloch Boston Biomedical Research Institute

R01 CA36207 Translation and Stability of Human Heat Shock mRNAs
Weber University of South Florida

R01 CA39066 Embryonal Carcinoma Growth and Differentiation
Linney Duke University

R01 CA39294 The Cytological and Physiological Mode of AP4A Action
Rapaport Boston University

R01 CA39931 Phenotypic Variation and Neoplastic Progression
Peterson John Muir Memorial Hospital, California

T-RNA (H)

R01 CA13591 Chemical Studies on Tumor Nucleic Acids
Randerath Baylor College of Medicine

R01 CA20683 Control Mechanisms in Human Tumor Cells--Small RNAs
Eliceiri St. Louis University

R01 CA20919 tRNA Q Base Metabolism in Normal and Tumor Cells
Katze University of Tennessee Center for Health Sciences

R01 CA28395 tRNA Methylation in Normal and Neoplastic Rat Tissues
Leboy University of Pennsylvania

R23 CA37836 Tumor Specific Differences in tRNA Methyltransferases
Reinhart Philadelphia College of Pharmacy-Science

R23 CA38015 Base-Pairing of Cytoplasmic LMW RNAs in Regulation
Maxwell North Carolina State University, Raleigh

DNA (I)

R01 CA14835 DNA Polymerases in Normal and Neoplastic Human Cells
Korn Stanford University

R01 CA15044 Pathogenetic Determinants of Human CNS Tumors
Manuelidis Yale University

R01 CA15187 DNA Synthesis: Regulation in Normal and Cancer Cells
Baril Worcester Foundation for Experimental Biology

R01 CA16790 DNA Transcription Control in Normal and Cancer Cells
Maio Yeshiva University

R01 CA23365 DNA Polymerases in Normal and Cancer Cells
Chang U.S. Uniformed Services Univ. of Hlth. Sci.

R01 CA24158 Rates of DNA Synthesis in Normal and Transformed Cells
Collins Virginia Commonwealth University

R01 CA26391 Molecular Pathology of Leukemia and Lymphoma
Coleman University of Kentucky

R01 CA34462 Role of Double Minutes and HSR Markers in Tumor Cells
George University of Pennsylvania

R01 CA34784 The Molecular Genetics of DHFR Gene Expression
Melera Sloan-Kettering Institute for Cancer Research

R23 CA34898 Cytoskeletal and Membrane Associations of B-Cell Ig
Rosenspire Sloan-Kettering Institute for Cancer Research

R23 CA35703 Cytoplasmic Control of Normal and Neoplastic Cell Growth
Gutowski University of Connecticut Health Center

R01 CA39365 Isolation of Amplified Genes from Human Tumors
Roninson University of Illinois at Chicago

R01 CA42047 Amplified Genes in Differentiation-Resistant HL-60 Cells
Gallagher Montefiore Medical Center

GROWTH FACTORS (J)

R01 CA11176 Factors Required for Mammalian Cell Division
Holley Salk Institute for Biological Studies

R01 CA15744 Spontaneous Transformation and Progression in Cell Lines
Rubin University of California, Berkeley

R01 CA16816 Mechanism of Chemical Carcinogenesis In Vitro
Moses Mayo Foundation

R01 CA21566 Anti-Tumor Invasion Factors Derived From Cartilage
Kuettner Rush University

R01 CA22410 Ceruloplasmin and Copper Metabolism in Cancer
Linder California State University, Fullerton

R01 CA23043 Peptide Transforming Factors from Transformed Cells
Ozanne University of Texas Health Science Center, Dallas

R01 CA24071 Studies of the Receptor for Epidermal Growth Factor
Carpenter Vanderbilt University

R01 CA25820 Growth Factor Receptors on Normal and Neoplastic Cells
Schlessinger Weizmann Institute of Science

R01 CA27217 Growth Factors and Receptors in Chemical Transformation
Moses Mayo Foundation

R01 CA27466 Endothelial Colony-Stimulating Activity
Quesenberry University of Virginia, Charlottesville

R01 CA28110 Nerve Growth Factor Function--Secretion by Cancer Cells
Young University of Florida

R01 CA29101 Characterization of a Liver Specific Growth Promotor
La Brecque University of Iowa

R01 CA30101 Structure and Function of Platelet-Derived Growth Factor
Antoniades Center for Blood Research

R01 CA30479 Mononuclear Phagocyte-Derived Growth Factor
Gillespie University of North Carolina, Chapel Hill

R01 CA31615 Growth Factors in Normal and Neoplastic Hematopoiesis
Adamson University of Washington

R01 CA33209 Leech Antimetastatic Factors: Isolation and Action
Gasic Pennsylvania Hospital

R01 CA34162 Growth Factors and Cellular Transformation
Scher Children's Hospital of Philadelphia

R01 CA34470 The Role of Epibolin and Serum in Cancer Cell Spreading
Stenn Yale University

R01 CA34472 Ca Growth Control in Neoplastic and Nonneoplastic Cells
Tucker Johns Hopkins University

R23 CA34590 Biochemistry of a Melanoma Growth Stimulation
Richmond Emory University

R01 CA34610 Intracellular Targets of Transforming Growth Factors
Massague University of Massachusetts Medical School

R01 CA34809 Tumor Promotion and Epidermal Growth Factor Receptors
King University of Illinois at Chicago

R01 CA35373 Hepatopoietins, Liver Regeneration and Carcinogenesis
Michalopoulos Duke University

R01 CA36306 Monokines Which Regulate the Production of CSA
Bagby Oregon Health Sciences University

R01 CA36544 Synthetic Transforming Growth Factors
Tam Rockefeller University

R01 CA36740 Regulation of Myelopoiesis by Acidic Isoferritins
Broxmeyer Indiana University-Purdue University at Indianapolis

R23 CA36908 Growth Factors and Human Bladder Cancer
Messing University of Wisconsin, Madison

R01 CA37392 Cartilage and Chondrosarcoma-Derived Growth Factors
Klagsbrun Children's Hospital (Boston)

R01 CA37393 Growth and Migration of Capillary Endothelial Cells
Zetter Children's Hospital Medical, Boston

R01 CA37395 Angiogenesis: A Control Point in Animal and Human Tumors
Folkman Children's Hospital (Boston)

R01 CA37754 Metabolism of the EGF-Receptor
Decker Rockefeller University

R01 CA38684 Autostimulation in Human Hemopoietic Neoplasia
Schrader Walter and Eliza Hall Institute of Medical Research

R01 CA38784 Platelet-Derived Growth Factor in Human Malignancies
Pantazis Center for Blood Research

R01 CA38808 Role of Platelet-Derived Growth Factor in Cell Growth
Huang St. Louis University

R23 CA38884 Mediators of the Humoral Hypercalcemia of Malignancy
Ibbotson University of Texas Health Science Center, San Antonio

R01 CA38981 Somatomedin Actions in Normal and Transformed Cells
Furlanetto Children's Hospital of Philadelphia

R01 CA39053 Growth Regulation of Polyamine Synthesis
Morris University of Washington

R01 CA39099 Cytoplasmic Factors in Cellular Growth
Bucher Massachusetts General Hospital

R01 CA39181 Cellular Actions of Transforming Growth Factors
Magun Oregon Health Sciences University

R01 CA39235 Tyrosine Phosphorylation and the Control of Cell Growth
Frackelton Roger Williams General Hospital

R01 CA39461 Angiogenesis-Inhibitor-Active Heparin Hexasaccharides
Albersheim University of Colorado

R01 CA39666 The Receptor for PDGF
Hood California Institute of Technology

R01 CA39911 Fibroblast Growth Factor and Neoplastic Transformation
Shipley Mayo Foundation

R01 CA40163 Mechanism of Action of a Human Granulopoietin
Gasson University of California

R01 CA40124 Functional Characterization of the Isolated PDGF Receptor
Owen Harvard School of Public Health

R01 CA40573 Molecular Studies of Transforming Growth and Factors
Donoghue University of California, San Diego

R23 CA40566 Hematopoietic Regulation and the Marrow Microenvironment
Gualtieri University of Alabama

R01 CA40597 Hemopoietic Cell Regulation in Leukemia
Hines Trudeau Institute, Inc.

NUCLEUS (K)

R01 CA12226 Metabolism of NC-Methylarginines and Neoplasia
Paik Temple University

R01 CA12877 Function of H1 Histone Phosphorylation
Langan University of Colorado Health Sciences Center

R01 CA15135 Histones in Cell Differentiation and Carcinogenesis
Zweidler Fox Chase Cancer Center

R01 CA17782 Tumor-Enriched Nonhistone Chromatin Proteins
Reeck Kansas State University

R01 CA28679 Chromosomal Organization of Dihydrofolate Reductase Gene
Biedler Sloan-Kettering Institute for Cancer Research

R01 CA29476 Clonal Karyotypic Evolution in Human Solid Tumors
Trent University of Arizona

R01 CA33011 Chromatin Proteins of Embryonal Carcinoma Cells
Oshima La Jolla Cancer Research Foundation

R01 CA34003 Nuclear cAMP Binding Proteins in Morris Hepatomas
Rosenberg Albany Medical College

R01 CA34775 Mapping Chromosomes and Genes in Relation to Leukemia
Chaganti Sloan-Kettering Institute for Cancer Research

R01 CA34783 Monoclonal Antibodies to Mitotic Cells
Rao University of Texas System Cancer Center

R23 CA34831 Gene Mapping of Chromosome 3 and Small Cell Carcinoma
Miller University of Colorado Health Sciences Center

R01 CA35829 Histone in Virally-Infected and Transformed Cells
Jackson Medical College of Wisconsin

R01 CA36468 High Resolution Chromosome Analysis of Acute Leukemia
Testa University of Maryland at Baltimore

R01 CA37193 Human Leukemia/Lymphoma Specific Changes in Chromatin
Mears Columbia University

R01 CA40189 Nuclear Targeting of Protein
Richter Worcester Foundation for Experimental Biology

CONTRACTILE ELEMENTS (L)

R01 CA05493 Leukopoietic Mechanisms
De Bruyn University of Chicago

R01 CA15544 Effect of Microtubular Proteins on Cell Surfaces
Berlin University of Connecticut Health Center

R01 CA16707 Tubulin Associations and Effects of Anticancer Drugs
Timasheff Brandeis University

R01 CA29405 Studies on Prostacyclin and Tumor Metastasis
Honn Wayne State University

R01 CA31760 Intermediate Filaments in Normal and Transformed Cells
Goldman Northwestern University

R01 CA33265 Tropomyosin Subunits: Normal and Transformed Cells
Warren University of Miami

R01 CA34282 Biochemical Mechanisms of Cellular Invasion
Rifkin New York University

R01 CA34709 Lymphoma Metastasis/Role of Endothelial Cell Recognition
Butcher Stanford University

R01 CA34763 Mutant B-Actin Gene Structure and Function in Neoplasia
Leavitt Linus Pauling Institute of Science and Medicine

R01 CA35738 Tropomyosins in Normal and Transformed Cells
Matsumura Cold Spring Harbor Laboratory

R23 CA35954 Cytochalasin/Probes of Cytoskeletal Function
Krafft Syracuse University at Syracuse

R01 CA36498 Cytoskeleton-Associated Proteins of Lung Carcinomas
Bernal Dana-Farber Cancer Institute

R01 CA37233 The Centrosphere in Normal and Transformed Cells
Albrecht Northwestern University

R23 CA38675 Regulation of Tubulin Biosynthesis
Lau Johns Hopkins University

R01 CA38729 Dynamics of Cancer Cell Traffic in the Lymphatic System
Weiss New York State Department of Health

R23 CA38915 Analysis of Novel Mammalian Cytoskeletal Polypeptides
Price University of California

R23 CA39510 Matrix-Mediated Tumor Cell Migration and Metastasis
McCarthy University of Minnesota, Minneapolis-St. Paul

R01 CA39755 Mechanism of Segregation of Modified Tubulin In Vivo
Bulinski University of California, Los Angeles

R01 CA41424 Studies of Mitosis in Normal and Neoplastic Cells
Brinkley University of Alabama at Birmingham

DEVELOPMENT AND DIFFERENTIATION (M)

R01 CA02662 Investigations on Teratocarcinogenesis
Stevens Jackson Laboratory

R01 CA10095 Gene Action and Cellular Differentiation in Culture
Silagi Cornell University Medical Center

R01 CA13047 Control Mechanisms of Differentiation and Malignancy
Friend Mount Sinai School of Medicine

R01 CA13533 Ectopic Placental Proteins in Cancer
Sussman Stanford University

R01 CA14054 Malignant Behavior and Cellular Antigen Expression
Klein Caroline Institute

R01 CA15619 Normal and Malignant Hematopoietic Cell Replication
Cline University of California, Los Angeles

R01 CA16368 Control of Differentiation of Erythroleukemic Cells
Skoultchi Yeshiva University

R01 CA16720 Gene Regulation and Interaction--Normal and Malignant Cells
Klinger Yeshiva University

R01 CA16754 Hybridization DNA Function Mutation in Cell Culture
Littlefield Johns Hopkins University

R01 CA17389 C-Cell Hyperplasia and Medullary Thyroid Carcinoma
Wolfe Tufts University

R01 CA17575 Erythroid Differentiation in Friend Leukemia Cells
Housman Massachusetts Institute of Technology

R01 CA18375 Hemopoietic Stem Cells and Induced Differentiation
Goldwasser University of Chicago

R01 CA19492 Terminal Transferase in Mammalian Hemopoietic Tissue
Coleman University of Kentucky

R01 CA21967 Normal/Neoplastic Phosphatases: Comparative Structures
Fishman La Jolla Cancer Research Foundation

R01 CA22294 Quantitative Studies on Granulocyte Differentiation
Kinkade Emory University

R01 CA22556 Differentiation of Granulocytes and Macrophages
Metcalf Walter and Eliza Hall Institute of Medical Research

R01 CA23097 Embryo-Derived Teratocarcinoma
Damjanov Hahnemann University

R01 CA25098 Alpha-Fetoprotein Regulation in Fetal and Cancer Liver
Chiu University of Vermont and State Agriculture College

R01 CA25512 Modulators of Granulopoiesis from Human Cell Lines
Brennan University of Rochester

R01 CA25966 X-Chromosome Activity in Teratocarcinoma Stem Cells
Martin University of California, San Francisco

R01 CA25972 Self-Renewal in Normal/Leukemic Hemopoietic Stem Cells
Metcalf Walter and Eliza Hall Institute of Medical Research

R01 CA26038 Differentiation and Proliferation of Myeloid Cells
Koeffler University of California, Los Angeles

R01 CA26656 Cell Culture Analysis of Human Epithelial Neoplasia
Rheinwald Dana-Farber Cancer Institute

R01 CA28050 Regulation of Alpha-Fetoprotein Gene Expression
Tilghman Institute for Cancer Research

R01 CA28427 EGF and Its Receptors in Embryonic Differentiation
Adamson La Jolla Cancer Research Foundation

R01 CA28656 Differentiation of Capillary Endothelial Cells
Auerbach University of Wisconsin, Madison

R01 CA31945 K-562: A Human Pluripotent Leukemia Stem Cell Line
Lozzio University of Tennessee, Knoxville

R01 CA32152 Growth and Differentiation of Human Melanocytes
Eisinger Sloan-Kettering Institute for Cancer Research

R01 CA32186 REC-DNA Analysis of Human Hematopoietic Differentiation
Salser University of California, Los Angeles

R01 CA33000 Glycoproteins in Differentiation and Oncogenesis
Fukuda La Jolla Cancer Research Foundation

R01 CA33021 Isolation of Tumor Genes from Human Lung Carcinomas
Perucho State University of New York, Stony Brook

R01 CA33065 Immunobiology of UVL-Induced Tumors
Daynes University of Utah

R01 CA33579 Growth and Differentiated Function of Keratinocytes
Green Harvard University

R01 CA33664 The In Vitro and In Vivo Regulation of Hemopoiesis
Cronkite Associated University-Brookhaven National Laboratory

R01 CA33800 Pathobiology of Chemically Induced Teratocarcinoma
Speers University of Colorado Health Sciences Center

R01 CA33895 Glycoproteins in Normal and Leukemic Cell Differentiation
Fukuda La Jolla Cancer Research Foundation

R01 CA34230 Onco-Developmental Gene Control: Alpha-Fetoprotein
Sell University of Texas Health Science Center, Houston

R01 CA34759 Molecular Basis of Oncogenesis and Differentiation
Tereba St. Jude Children's Research Hospital

R01 CA34826 Oncogenes and Growth Factors in Pre-B Cells
Ozanne University of Texas Health Science Center, Dallas

R01 CA34891 Molecular Basis of Differentiation and Neoplasia
Roeder Rockefeller University

R01 CA35150 Chromosome Translocations and Ig Genes in Human Leukemia
Nowell University of Pennsylvania

R01 CA35326 Expression of Exogenous Genes in Teratocarcinoma
Gautsch Scripps Clinic and Research Foundation

R01 CA35367 Embryonic Control of Neuroblastoma and Melanoma
Pierce University of Colorado Health Sciences Center

R01 CA35517 The Role of cAMP in Leukemic Cell Differentiation
Fontana West Virginia University

R01 CA35533 Epigenetic Regulation of the Chondrosarcoma
Miller University of Colorado Health Sciences Center

R01 CA35823 Human Lymphocytic Leukemia Oncogenes/Gene Products
Kennett University of Pennsylvania

R01 CA36122 Neuroblastoma Transfection and Transformation
Gilbert Mount Sinai School of Medicine

R01 CA37675 Teratocarcinoma Stem Cell Adhesion
Grabel Wesleyan University

R23 CA37727 Induction of Leukemic Cell Maturation
Tsiftsoglou Beth Israel Hospital, Boston

R01 CA37874 Effect of Proteases in Erythroid Cell Differentiation
Scher Mount Sinai School of Medicine

R23 CA37887 Malignant Potential of the Components of Wilm's Tumors
Garvin Medical University of South Carolina

R01 CA37918 Hemin Transport into Differentiating Leukemic Cells
Glass Beth Israel Hospital, Boston

R01 CA38189 Bone-Bone Marrow Interaction
Lee University of Washington

R01 CA38405 Activation of Primordial Germ Cells to Form Teratomas
Damjanov Hahnemann University

R23 CA38972 Glycosaminoglycans and Differentiation of Human Leukemia
Luikart University of Minnesota, Minneapolis-St. Paul

R01 CA39017 Cell Lineages in Normal and Preneoplastic Mammary Growth
Medina Baylor College of Medicine

R01 CA39036 Retinoic Acid--Role in Differentiation and Carcinogenes
Gudas Dana-Farber Cancer Institute

R01 CA39131 Developmental Variants of Embryonal Carcinoma Cells
Moore National Jewish Hospital and Research Center

R01 CA39192 DNA Rearrangements at the MYC Locus in Myeloma Tumors
Cole Princeton University

R23 CA39436 Differentiation of Cervical Epithelial Cells
Wright Harvard University

R01 CA39924 The Controlled Initiation of Neoplasm in Drosophila
Hanratty University of California, Irvine

R01 CA40165 A-System Amino Acid Transport and Protein Kinase C
Cook Martin Marietta Energy Systems, Inc.

R01 CA40575 Hemopoietic Stem Cell Proliferation and Formation
Van Zant Texas Tech. University Health Sciences Center

R01 CA41425 Endocrine Regulation of Melanoma Cell Differentiation
Fuller University of Oklahoma Health Sciences Center

CELL GROWTH, CELL DIVISION (N)

R01 CA06663 Mechanisms of Control of Mammalian Cell Multiplication
Lieberman University of Pittsburgh

R01 CA15062 Studies of Normal and Neoplastic Prostate
Ahmed University of Minnesota of Minneapolis-St. Paul

R01 CA16463 Thyroid Hormone Effects on Cell Regulation
Surks Montefiore Hospital and Medical Center

R01 CA22042 Molecular Analysis of Progression Through G1
Stiles Dana-Farber Cancer Institute

R01 CA24193 Regulation of Mammalian Cell Cycle
Pledger University of North Carolina, Chapel Hill

R01 CA24385 Effects of Phorbol Esters on Lymphocyte Stimulation
Mastro Pennsylvania State University, University Park

R01 CA25898 Analysis of G1 in Mammalian Cells
Baserga Temple University

R01 CA27399 Regulation of Mitosis in Normal and Transformed Cells
Sisken University of Kentucky

R01 CA27544 Purification and Characterization of Mitotic Factors
Rao University of Texas System Cancer Center

R01 CA27564 Methionine Dependence--A Metabolic Marker in Cancer
Hoffman University of California, San Diego

R01 CA28240 Pathology in Cell Cycle Control of Differentiation
Scott Mayo Foundation

R01 CA33505 Cell Cycle Specific Control of Cellular Differentiation
Yen University of Iowa

R01 CA33764 Analysis of Melanoma Growth and Regression
Amoss Texas Agri. and Mech. University College Station

R01 CA34460 Cell Cycle Control--The Role of Monovalent Cation Fluxes
Adelberg Yale University

R01 CA34512 Regulation of 2-5A-Dependent RNase Levels By Interferon
Silverman U.S. Uniformed Services Univ. of Hlth. Sci.

R01 CA35469 Collagenase Function and Activity in Malignant Tumors
Takahashi Yeshiva University

R01 CA35789 Regulation of Gene Expression by Interferons
Sen Sloan-Kettering Institute for Cancer Research

R01 CA36063 Malignant Tumor Metastasis: Role of Vitamin K Metabolism
Fasco New York State Department of Health

R01 CA36464 Myelopoietic Regulation By Lactoferrin and Transferrin
Broxmeyer Indiana University-Purdue University at Indianapolis

R01 CA36487 The Role of Calcium in Cell Growth Regulation
Dedman University of Texas Health Science Center, Houston

R01 CA36535 Regulation of Cellular Growth in Multicellular Spheroids
Freyer University of California

R01 CA36784 Calcium and Cell Cycle Control in Human Fibroblasts
Tupper Syracuse University at Syracuse

R01 CA36913 Biology and Therapy of Poorly Nourished Tumor Cells
Tannock Ontario Cancer Treatment and Research Foundation

R01 CA37391 Anticoagulants, Vitamin K, and Tumor Cell Growth
Hauschka Children's Hospital, Boston

R01 CA37673 Regulation of Expression of the Thymidine Kinase Gene
Deininger Louisiana State University Medical Center, New Orleans

R01 CA37789 Polyamine Metabolism and Colon Cancer
Luk Johns Hopkins University

R01 CA38016 Altered Nutritional Requirements for Growth
McClure W. Alton Jones Cell Science Center

R01 CA39712 Regulation of Adenylate Cyclase Upon Transformation
Manning University of Pennsylvania

R01 CA40332 Studies on Mammalian Cell Proliferation
Soprano Temple University

METASTASIS (O)

R01 CA36547 The Role of Cell Movement and Contact in Tumor Invasion
Bell University of Oklahoma, Norman

R01 CA38931 Characteristics Associated with Invasive Human Tumors
Kupchik Boston University

R01 CA40351 Properties of Emerging Metastatic Tumor Cell Variants
Kimura University of Florida

SOMATIC CELL GENETICS (P)

R01 CA12130 Cytoplasmic Inheritance in Normal and Tumor Cells
Harris University of California, Berkeley

R01 CA19401 Genetic Analysis of Human Malignancy
Stanbridge University of California, Irvine

R01 CA30938 Structural and Functional Analysis of Cloned MHC Gene
Weissman Yale University

R01 CA31472 Mechanism of Gene Regulation in Somatic Cell Hybrids
Papaconstantinov University of Texas Medical Branch, Galveston

R01 CA31777 BUDR Dependence, Malignancy, and Differentiation
Davidson University of Illinois at Chicago

R01 CA31995 Retroviral Oncogenes: Analysis of Cellular Homologues
Sheiness Louisiana State Univ. Med. Ctr., New Orleans

R01 CA32580 Biochemical Genetics of Mammalian Nucleoside Transport
Ullman University of Kentucky

R01 CA33108 Characterization of Lymphoid and Myeloid Transforming Genes
Lane Dana-Farber Cancer Institute

R01 CA40202 Pathogenesis of Human Pre B-Cell Leukemias
Croce The Wistar Institute

INHERITANCE OF NEOPLASMS (Q)

R01 CA33093 Recombinant Inbred Mouse Strains and Cancer
Taylor Jackson Laboratory

PLASMIDS, VIRUSES (R)

R01 CA11526 Tumor-Inducing Substance of Agrobacterium Tumefaciens
Kado University of California, Davis

IN VIVO AND IN VITRO TUMOR LINES (S)

R01 CA24145 Ovarian Tumors in Young Mice
Beamer Jackson Laboratory

R01 CA29078 Cellular Origins of Hepatic Preneoplasias
Iannaccone Northwestern University

R01 CA32722 Research in Surgical Oncology: Colon Cancer
Aust University of Texas Health Sciences Center, San Antonio

R01 CA33027 Differentiation and Chemotherapy in Human Gliomas
Yung University of Texas System Cancer Center

R01 CA33305 Genetic Basis for Spontaneous Cancer and Aging
Rodriguez University of Texas System Cancer Center

R23 CA37238 Regulation of Pituitary Hyperplasia and Neoplasia
Lloyd University of Michigan at Ann Arbor

R01 CA37778 Polyamine Metabolism and Colon Cancer
Luk Johns Hopkins Unversity

R01 CA38110 Pathobiology of Metastasis in a New Melanoma Model
Berkelhammer AMC Cancer Research Center and Hospital

R01 CA38889 Human Mammary Cells: Modulation of Differentiated State
Bartley University of California

CONFERENCES (T)

R13 CA02809 Cold Spring Harbor Symposia on Quantitative Biology
Watson Cold Spring Harbor Laboratory

R13 HD20793 Conference on Tissue Specific Expression of Cloned Genes
Slavkin University of Southern California

R13 AI21618 Symposium on Genetic Control of Host Resistance
Skamene Medical College of Georgia

R13 GM35234 Gordon Research Conference on Molecular Genetics
Woo Gordon Research Conferences

R13 AM35735 Gordon Research Conference on Hormone Action
Bardin Gordon Research Conferences

R13 CA38585 Gordon Research Conference on Fibronectin
Ruoslahti Gordon Research Conferences

R13 CA38652 1985--Conference on Leukemia
Fox University of California, Los Angeles

R13 CA39497 Differentiation of Normal and Neoplastic Cells
Pierce University of Colorado Health Sciences Center

R13 CA39990 Mechanism of Carcinogenesis
Sherr Federation of American Societies

R13 CA40848 Gordon Research Conference on Cancer, 1985
Stanbridge Gordon Research Conferences

R13 CA40849 Conference on Cell Contact and Adhesion
Steinberg Gordon Research Conferences

SMALL BUSINESS GRANTS (U)

R44 CA36656 Microcarriers from Inorganic Materials
Hillegas KMS Fusion, Inc.

R43 CA40853 A Standard Human DNA Repository
Kouri International Biotechnologies, Inc.

R43 CA40868 DNA Probes for Detection of Chromosomal Translocations
Heisterkamp Oncogene Science, Inc.

PROGRAM PROJECTS (V)

P01 CA10893 Cancer Research Center
Busch Baylor College of Medicine

P01 CA21901 Studies of Normal and Malignant Cell Membranes
Roseman Johns Hopkins University

P01 CA22376 Control of Gene Expression: Normal and Neoplastic
Feigelson Columbia University

P01 CA22427 Molecular Analysis of Malignant Transformation
Pardee Dana-Farber Cancer Institute

P01 CA23076 Regulatory Mechanisms in Tumor Biology
Mueller University of Wisconsin, Madison

P01 CA25875 Cell Differentiation and Cancer
Croce Wistar Institute of Anatomy and Biology

P01 CA26712 Molecular Analyses of Cellular Proteins and Their Genes
Hynes Massachusetts Institute of Technology

P01 CA28896 Cell-Matrix Interactions in Neoplasia and Development
Ruoslahti La Jolla Cancer Research Foundation

P01 CA29545 Interferon, Differentiation and Oncogenesis
Carter Hahnemann Medical College & Hospital of Philadelphia

P01 CA29569 Gene Organization and Expression in Eukaryotes
Sambrook Cold Spring Harbor Laboratory

P01 CA31768 Leukemia Cell Systems: Induction of Differentiation
Rifkind Sloan-Kettering Institute for Cancer Research

P01 CA32737 A Program in Medical Oncology
Golde University of California, Los Angeles

P01 CA34936 A Mutational Model for Childhood Cancer
Strong University of Texas System Cancer Center

P01 CA37589 Cell Culture Factors and Their Relation to Cancer Biology
Sato W. Alton Jones Cell Science Center

DIFFICULT-TO-CLASSIFY (W)

R01 CA09247 Partial Subsidy for the Journal of Cancer Research
Handschumacher American Association for Cancer Research

R01 CA22062 A Bone Resorptive Protein from Cancer Ascites Fluid
Nimberg Boston University

R01 CA25298 Biology of Human Cutaneous Malignant Melanoma
Clark University of Pennsylvania

R01 CA38645 The Effect of Gallium on Bone
Bockman Sloan-Kettering Institute for Cancer Research

R01 CA39040 Biochemical Pathology of Iron Storage in Liver Cancer
Massover University of Medicine and Dentistry of New Jersey

R01 CA40330 Stress Proteins, Drug Tolerance and Cellular Deprivation
Subjeck New York State Department of Health

ONCOGENES/TRANSFECTION (X)

R01 CA26663 Cell Transformation by RSV
Weintraub Fred Hutchinson Cancer Research Center

R01 CA28946 Transfection by Endogenous Human Transforming Genes
Cooper Dana-Farber Cancer Institute

R01 CA35911 Expression and Structure of Invertebrate Oncogenes
Wadsworth Worcester Foundation for Experimental Biology Inc.

R01 CA36246 Chromosome Translocated Oncogenes and Neoplasia
Marcu State University New York, Stony Brook

R01 CA36327 Isolation of Transforming Genes in Murine Thymomas
Pellicer New York University

R01 CA36355 Expression of Oncogenes and IgA Genes in Transformed Cells
Sonenshein Boston University

R01 CA36827 Oncogenes in Physiologic and Pathologic States
Slamon University of California, Los Angeles

R01 CA36928 Structure-Function Studies of Altered Oncogenic Proteins
Buchanan Massachusetts Institute of Technology

R23 CA37038 Role of GTP in RAS Oncogene Induced Transformation
Halliday University of California, Berkeley

R01 CA37165 c-myc Rearrangements in Human Hematopoietic Neoplasias
Dalla-Favera New York University

R01 CA37222 Properties of Cellular and Viral SRC Genes
Parker Columbia University

R01 CA37351 Inhibition of Human Oncogene Expression
Friedman U.S. Uniformed Services University of Health Sciences

R01 CA37702 The Function of the ras Oncogene Homolog in Yeast
Tatchell University of Pennsylvania

R01 CA37866 Analysis of Human Oncogene Polymorphisms
Krontiris Tufts University

R01 CA38047 DNA Rearrangements in MoMULV Induced Thymomas
Tsichlis Fox Chase Cancer Center

R01 CA38635 onc Gene Introduction and Expression in Mice
Brinster University of Pennsylvania

R01 CA38783 The Role of c-myc and Other Oncogenes in Carcinogenesis
Lee University of California, San Francisco

R01 CA38876 Structural and Genetic Analysis of ras p21 Function
Goldfarb Columbia University

R01 CA38901 Oncogene Regulation in Malignant Cells
Klinger Albert Einstein College of Medicine

R01 CA39186 Genetics of Hematopoietic Cancers
Sakaguchi University of Texas Health Science Center, San Antonio

R01 CA39550 Regulation and Function of the c-myc Oncogene
Cole Princeton University

R01 CA39811 Transformation by Human ras Oncogenes
Feramisco Cold Spring Harbor Laboratory

R01 CA39849 Function of Yeast Oncogene Homologues
Broach Princeton University

R01 CA39964 Transforming Proteins of Nonvirally Induced Tumors
Weinberg Whitehead Institute for Biomedical Research

R01 CA40002 Activation of p53 Gene in Tumor Cells
Rotter Weizmann Institute of Science

R01 CA40099 Functional Analysis of the p53 Cellular Tumor Antigen
Oren Weizmann Institute of Science

R23 CA40242 Role of Oncogenes in Erythroid Differentiation
Lachman Yeshiva University

R01 CA 40364 Expression of Translocated c-myc in B-Cell Tumors
Hayday Yale University

R01 CA40402 The Transforming Potential of Cellular Oncogenes
Sawicki The Wistar Institute

R23 CA40533 Molecular Study of Transforming Genes in Murine Lymphomas
Newcomb New York University Medical Center

R01 CA40540 Neoplastic Transformation by ras Oncogenes
Corces Johns Hopkins University

R01 CA40572 Detection and Analysis of onc Genes in Defined Media
Scangos Johns Hopkins University

R01 CA40582 Effect of myc-Gene Expression on Growth in Lung Cancer
Sorenson Dartmouth College

R01 CA40602 Oncogene Collaborations in Cell Transformation
Ruley Massachusetts Institute of Technology

R01 CA40620 Molecular Studies of Variation in ras Oncogene Proteins
Furth Sloan-Kettering Institute for Cancer Research

R01 CA40636 Deregulation of Oncogene Expression in Human Tumors
Astrin Institute for Cancer Research

R01 CA41629 The Genetics and Biochemistry of the ras Pathway
Wigler Cold Spring Harbor Laboratory

R01 CA41996 Structural and Functional Analysis of Yeast ras Proteins
Tamanoi University of Chicago

OUTSTANDING INVESTIGATOR GRANTS (Y)

R35 CA39814 Genomic Changes in Cancer: Mechanisms and Consequences
Sager Dana-Farber Cancer Institute

R35 CA39825 Sex Hormones and Cancer
Siiteri University of California

R35 CA39829 Genetics of Cell Proliferation
Wigler Cold Spring Harbor Laboratory

R35 CA39860 Genetics of Human Hematopoietic Neoplasias
Croce The Wistar Institute

R35 CA40029 Terminal Differentiation of Epidermal and Adipose Cells
Green Harvard Medical School

IMMUNOLOGY PROGRAM

The Immunology Program of the National Cancer Institute supports research that contributes to an understanding of the role of the immune system in the development, growth and spread of tumors. The specific areas of investigation supported by the Program include:

- The synthesis and structure of myeloma proteins in animals and man.

- The synthesis, structure, and function of antibodies capable of reacting with tumor cells, agents which induce tumors, and agents used in the treatment of tumors.

- The synthesis, structure, and function of humoral factors other than antibody which participate in, activate and/or regulate the immune response to tumors. This would include complement, interferon, lymphokines, lymphoid cell growth factors, helper factors, suppressor factors, etc., as they are involved in immune responses to tumors.

- The immunobiology of lymphocytes which participate in antitumor responses including their development, heterogeneity, interactions, and functions.

- The immunobiology of monocytes and macrophages which participate in antitumor responses including their development, heterogeneity, interactions, and functions.

- The identification, isolation, and characterization of cell surface determinants of lymphocytes and macrophages which are involved in the responses of these cells to tumors.

- The identification, isolation, and characterization of cell surface determinants on tumor cells which serve as target antigens for the immune response.

- The immunobiology of malignancies of the immune system (lymphomas and leukemias) including studies of immunologic markers for the classification and characterization of neoplastic cells and their normal counterparts.

- Immunobiology of sarcomas, carcinomas, and melanomas including studies of immunologic markers for the classification and characterization of tumor cells and their normal counterparts.

- Immune surveillance against the development of tumors of various origins by all immune mechanisms (e.g. T cell-mediated immunity, macrophage reactivity, natural killer cell activity).

- Immunopathology studies on the host-tumor interaction.

- Immune status of tumor-bearing animals and man including studies on immunostimulation, immunosuppression, and the effects of disease course on immune function.

- Bone marrow transplantation (BMT) in man and animals as a treatment for cancer when the emphasis is on understanding how BMT affects or is affected by the immune system.

- Immunotherapy in animal models including studies on specific and nonspecific stimulation of the immune system using natural and synthetic agents when the emphasis is on understanding how the therapy affects or is affected by the immune system.

- Immunotherapy including preclinical and clinical protocols where the main emphasis is upon the study of immune parameters, immune mechanisms, and other immunologic concerns rather than upon a therapeutic result. Included are studies on specific and nonspecific stimulation of the immune system using natural and synthetic agents.

The Immunology Program supports a broad spectrum of research in the areas of basic immunology and tumor immunology. The number of grants funded in each category with their costs are identified in Table 1 of this report. Since the Immunology Program funded 395 grants and expended approximately 60 million dollars during FY 1985, this report serves to highlight selected areas of research and should not be considered comprehensive.

Last year, the Immunology Program Annual Report focused on current research on cytotoxic lymphocytes, since recent availability of specific monoclonal antibodies had made possible many studies on the biochemical nature and functional reactivity of lymphocyte cell surface determinants which mediate immune function. Included were initial findings which led to the breakthrough in the

discovery of the elusive T-cell receptor for antigen. This research area has been highly active and intensively competitive this year, and this report will summarize some of the important findings in this rapidly moving research area.

In addition to the well-studied and characterized cytotoxic lymphocyte response, new research is demonstrating additional, previously unrecognized components of the immune system. This report will summarize some recent studies on the immune function of the skin, an organ not previously thought to play an active role in the immune response.

Research on the immunologic aspects of the Acquired Immune Deficiency Syndrome (AIDS) will be updated. As this area has been reviewed in previous annual reports, this report will serve mainly to summarize recent research and to describe some additional, yet controversial, hypotheses for the pathogenesis of this disease.

In conclusion, a few noteworthy findings will be mentioned as points of interest, but will not be covered in detail in this report. As these research areas progress, they may be reviewed in depth in future reports.

T-CELL RECEPTORS

Last year we reported that James Allison (CA 26321) and his colleagues obtained "clonotypic" molecules from T lymphocytes which were suggested to be candidates for the elusive antigen-binding T-cell receptor (TcR; Allison et al., 1982). Following Dr. Allison's finding, a number of exciting new developments took place which are going to have a substantial impact on tumor immunology and cancer research in general. This report focuses on the contribution of investigators supported by the Immunology Program, DCBD to the recent progress in the following TcR-related areas: 1) Isolation and characterization of T-cell specific clonotypic and allotypic molecules from human and murine T cells; 2) Isolation and sequencing of human and mouse cDNA clones encoding T-cell specific membrane proteins; 3) Studies on the rearrangement of TcR genes during intra-thymic ontogeny and T-cell differentiation; 4) Elucidation of the structure and function of TcR-associated cell surface components; 5) Delineation of chromosomal location for genes coding for TcR; 6) Studies on the specificity of antigen and MHC binding to TcR; 7) Application of the newly acquired knowledge on TcRs to the diagnosis and therapy of immunoregulatory disorders and various forms of T-cell neoplasia.

Isolation and Characterization of TcR

The suggestion that the clonotypic heterodimer, defined by Dr. Allison and his collaborators, was indeed the TcR, was supported by results obtained independently by other groups. Similar findings were reported in human cells by Ellis Reinherz, Stuart Schlossman (CA 25369) and their collaborators, who produced clonotypic antibodies inhibiting two T-cell lines with Class I and

Class II MHC reactivity. In both cases, the target structure was a disulfide-linked heterodimer, composed of 43-50 kd subunits (Meuer et al., 1982a, 1983a,b). Henry Kunkel, David Posnett (CA 35463) and their collaborators have compared two different human T-cell leukemias using anti-clonotypic murine monoclonal antibodies. In each case, they obtained disulfide-linked heterodimers of about 43 kd. One of the leukemias responded with proliferation upon exposure to the anti-clonotypic reagent (Bigler et al., 1983; Posnett et al., 1984).

In the murine system, Frank Fitch (CA 19266) and his collaborators produced polyclonal and monoclonal antibodies with clone-specific effects on T cells (Lancki et al., 1983). Similarly, Charles Janeway (CA 29606) and colleagues produced clonotypic antibodies which specifically blocked the release of interleukin-2 (IL-2) by antigen-specific, Class II MHC-restricted murine T-cell lines. The cell-surface structures, reactive with the antibodies, were found to be disulfide-linked heterodimers of 40-50 kd subunits (Kaye and Janeway, 1984). Monoclonal antibodies to the receptors were shown to substitute for both the antigen and MHC in stimulating target cells, suggesting that the molecule recognized by these antibodies comprised the entire T-cell receptor (Kappler et al., 1983).

Concerning the identity of TcR in murine cytotoxic T lymphocytes (CTL), Herman Eisen (CA 15472, CA 28900), Susumu Tonegawa (CA 28900) and their colleagues produced clone-specific antisera in mice against cloned CTLs derived from BALB/c mice. The anti-clonotypic antisera inhibited CTL-mediated lysis of P815 target cells in a clone-specific manner. Antisera raised in rats against individual clones inhibited the cytotoxic activity of all clones. These alloantisera immunoprecipitated a disulfide-linked dimer (45 kd) from radiolabelled CTL (Kranz et al., 1984a).

Thus, the correspondence of the findings in various T cell lines in the human as well as in the murine systems strongly suggested that the alpha-beta heterodimer, detected independently by a number of groups, was the antigen/MHC-binding receptor of T cells.

Functional studies on TCR were hampered by the fact that anti-clonotypic antibodies are useful only when applied to the clones against which they were raised. Following a number of unsuccessful initial attempts, Dr. Allison and his collaborators were able to produce xenogeneic and allogeneic antisera as well as monoclonal antibodies against cross-reactive epitopes of TcRs (Allison et al., 1984). These antibodies were found to precipitate similar heterodimers from heterogenous mixtures of normal thymocytes and splenic T cells. In addition, Michael Bevan (CA 25803) and his collaborators have recently produced alloantisera and monoclonal antibodies in C57L mice against T lymphocytes obtained from BALB/c mice. This anti-allotypic antibody recognized about 25% of peripheral T cells in BALB/c mice. Moreover, it precipitated the same heterodimer as the rat monoclonal antibody that was produced against the isolated receptor molecule. The antigen defined by the anti-allotypic antibody is present on CTLs and this antibody can induce resting peripheral T lymphocytes to proliferate (Staerz et al., 1985).

The first indications that the subunits for TcR are similar to heavy (H) and light (L) chains of immunoglobulins (Igs), in the sense that they are composed of variable (V) and constant (C) segments, were obtained by Drs. Allison, Marrack and their collaborators. They produced proteolytic peptide fingerprints of the alpha-beta heterodimers obtained from lymphoma cells and compared them to those obtained from heterogenous normal thymocytes and splenic T cells. The peptide fingerprints for the alpha and beta chains were different, suggesting that both chains of TcR contain different C regions. Comparison of fingerprints obtained from clonal T cells with those from heterogenous normal lymphocytes suggested the presence of V and C regions (Kappler et al., 1983; Allison et al., 1984). Preliminary efforts to sequence the TcR from human T leukemia cells, against which Ian Trowbridge (CA 17733) had prepared a clonotypic monoclonal antibody, were unsuccessful, probably because they contained blocked N-termini (Kappler et al., 1983). However, sequencing of the tryptic and CNBr fragments resulted in a pentapeptide which was found to be identical with the sequence predicted to be present in the C region of a cDNA clone of a putative TcR.

Recombinant DNA Research on TcR

Perhaps the most important recent development in this field has been the isolation of human and mouse cDNA clones encoding membrane proteins that are uniquely expressed on T cells and the identification of rearranged TcR genes. This pioneering work was done independently and simultaneously by the groups of Drs. Eisen and Tonegawa for the alpha and gamma genes, and by Drs. Davis and Mak and their collaborators for the beta gene (Saito et al., 1984a,b; Yanagi et al., 1984; Hedrick et al., 1984). By using a novel technique of DNA cloning, known as subtractive hybridization, these groups looked for T-cell specific messages whose genomic sequences are rearranged in mature T cells. The sequences they found have shown a striking similarity to the organization of Ig genes, which suggested that the subunits of TcR molecules are made of two disulfide-linked domains, indicating the presence of "immunoglobulin folds" that distinguish the immunoglobulin family from other globular proteins. Marked sequence homology at several critical sites adjacent to the intra-chain bridges indicated that TcR and Igs are very similar. Comparison of several sequences has made it immediately clear that the N-terminal domain is variable and the C-terminal domain constant. Evidence was shown for independent J and D segments between the two domains. The pattern of amino acid residues deducted from different V sequences suggested a division of the V domain into hypervariable and framework sequences corresponding in locations to the equivalent sequences in the V regions of Igs. All the currently available data suggest that the variable domains of the alpha and beta chains interact with each other so that the hypervariable residues of the two chains are brought into juxtaposition forming a pocket or shallow groove of the combining site of TcR. Thus, the murine TcR was shown to resemble the first two domains of a "general" Ig chain to which a hydrophobic transmembrane segment and a short intracytoplasmic tail are attached.

These initial observations were soon followed by important new results on the organization and chromosomal localization of TcR genes and their expression during ontogeny and cellular differentiation. But first of all, the correspondence between the identity of TcR, obtained by biochemical techniques and the putative TcR sequences, suggested from analysis of cDNAs, had to be established. Drs. Trowbridge (CA 17733), Marrack, Freed (CA 36700) and their collaborators purified the alpha and beta chains of the receptor from a human T-cell leukemia line and determined the amino acid sequence of several tryptic peptides derived from each chain. Their results showed that cDNA clones reported by others indeed encode alpha and beta chains. In addition, the alpha chain peptide showed a remarkable homology to the conserved portion of the J segment of Igs and TcR beta chains (Hannum et al., 1984). Dr. Reinherz and his collaborators simultaneously reported their data on the sequence of the TcR alpha subunit (Fabbi et al., 1984; Acuto et al., 1984). Their analysis revealed 40% homology between a CNBr fragment of the alpha subunit and the third framework of the V region of kappa and lambda chains of Igs. The convergence of the two independent lines of investigations, biochemical and gene-cloning, provided strong evidence that the T-cell specific cDNA clones and the biochemically characterized heterodimer are, indeed, related to TcR.

A third T-cell specific sequence of cDNA, isolated by Drs. Eisen, Tonegawa and their collaborators, was first suggested to be an alpha chain. However, the putative gene product did not contain sites for N-glycosylation (Saito et al., 1984a). Therefore, the identity of this T-cell product was questioned because the alpha chain was shown to be a glycoprotein. Drs. McIntire and Allison investigated the synthesis and processing of murine TcR and found that the alpha and beta chains are dimerized shortly after translation, followed immediately by extensive glycosylation (McIntire and Allison, 1984). A minimum of three N-linked oligosaccharide side chains were found to be formed on each subunit. As a result of these findings, the gene product was reexamined and identified as a third (gamma) T-cell specific gene (Saito et al., 1984b; Kranz et al., 1985).

The function of the gamma chain is still not well defined. The rearranged gamma genes are transcribed only infrequently in helper T cells. It is present in all CTLs so far examined, suggesting that the product of the gamma gene is related to the specificity or differentiation of CTLs. It is possible that the product of the gamma gene is a "second receptor" or part of a "1 1/2 receptor" (Pernis and Axel, 1985). However, since no antiserum directed against the alpha-beta heterodimer has so far detected a third subunit (Allison et al., 1982; Meuer et al., 1983; Kranz et al., 1984; Staerz et al., 1985b), it is unlikely that the putative gamma chain is closely associated with the alpha-beta heterodimer. The gamma chain could be a minor isotype, similar to the lambda light chain of Ig which is also relatively invariant. A third possibility is that the gamma gene or its product has a temporary role in T-cell differentiation.

The layout of component TcR genes in the germ-line configuration was investigated by several groups and it was found that an upstream V region gene family is followed, at an unknown distance, by a tandem cluster of J-C

genes where each of two C region genes is preceded by a set of J sequences. Also, there is a cluster of J segments between the two C region genes (Malissen et al., 1984; Hedrick et al., 1985). The organization of the gamma gene consists of at least three V, three C and three J segments. In cloned CTL, one each of these fragments is rearranged and expressed as a VJC transcription unit (Hayday et al., 1985). The organization of the gamma gene family and the expressed gene product is very similar to the genes and products of the Ig loci. The C region of the gamma gene is similar to that of the beta chain of TcR. Also, the J segments have most homology to the corresponding J segments in the beta chain of TcR. In different T cells, the gamma chain is assembled from the same V and J segments, but it is diversified due to sequence variations in the junction of its rearranged V and J segments (Kranz et al., 1985).

Role of TcR in Ontogeny and T-Cell Differentiation

Intrathymic ontogeny of human T cells has been examined by Drs. Schlossman, Reinherz and their colleagues, using T-cell lineage-specific monoclonal antibodies (Reinherz et al., 1980). The earliest identifiable T-lineage cell expresses the T11 protein (Stage I). With maturation, T4, T6 or T8 molecules are coexpressed (Stage II). Eventually, the cortical T6 marker ceases and T3 is acquired. From this point on, thymocytes terminally differentiate in two directions, producing T3+ T4+ T8- or T3+ T4- T8+ cells (Stage III). The same group has demonstrated that the T4+ subset of cells (about 2/3 of peripheral blood lymphocytes) provides helper/inducer activities for T-T, T-B and T-macrophage interactions, whereas the T8+ subset constitutes suppressor cells. In order to study the expression of TcR genes during intrathymic ontogeny, the Reinherz group has now shown that rearrangement of the human TcR beta genes is detectable in Stage II but not in Stage I thymocytes. In contrast, the display of the alpha-beta heterodimer on the cell surface takes place only in Stage III (T3+) thymocytes (Acuto et al., 1985). Similar studies were done by the Marrack group who found a steady increase in the frequency of rearranged beta genes during intrathymic ontogeny. Fully rearranged beta genes did not appear until day 16 of fetal development, one day prior to the surface expression of the TcR protein (Boon et al., 1985).

To understand the relationship of the expression of the three TcR genes during ontogeny, David Raulet (CA 28900) and his collaborators studied the regulation of TcR gene expression in murine T cells. They found an abundance of mRNAs coding for the beta and gamma subunits in immature thymocytes, while the level of alpha mRNAs remained relatively low. During further maturation of thymocytes, while the level of alpha mRNA increased, that of gamma declined and beta stayed constant. These results indicate that the gamma gene product is involved in the early differentiation of T cells (Raulet et al., 1985). Similar temporal expression of the three genes was shown independently by another group (Snodgrass et al., 1985).

To determine whether different isotypes of TcR occur which are similar to the different classes of immunoglobulins, Dr. Reinherz and his colleagues studied the rearrangement of different beta chains in CTLs, as well as

in inducer and suppressor T cells. They found that the same beta gene was rearranged in functionally different T cells, suggesting that the isotype of T-cell subclasses is not determined by the beta genes (Royer et al., 1984). A somewhat different conclusion was reached by Dr. Bevan and his collaborators who examined the expression of the beta genes in different T-cell subsets and found that helper and CTL cells may use common beta chains whereas suppressor cells might not (Hedrick et al., 1985). The currently available data suggest that functional diversity of T-cell subsets is determined not by the constant regions of the alpha, beta and gamma chains, but by different accessory molecules such as T4 and T8.

Recent studies by the Reinherz group on the rearrangement and expression of TcR genes in natural killer (NK) cells have led to a more precise identification of this cell type. NK cells are large granular lymphocytes whose lineage has been uncertain because they express both T-cell and myeloid-associated cell surface markers. Dr. Reinherz and others have cloned NK cells from normal peripheral blood. A series of clones of these cells has now been characterized with respect to the expression of the alpha and beta TcR genes. It was found that the T3+ clones of NK cells contained both alpha and beta transcripts and expressed disulfide-linked heterodimers on their surface. Thus, the T3-positive NK cells seem to belong to the T cell lineage. However, the identity of T3-negative NK cells remains to be determined (Ritz et al., 1985).

TcR-Associated Molecules

The effects of T-cell lineage-specific antibodies on the function of different T-cell lines have implicated additional monomorphic structures which are associated with TcR in the mediation and transduction of extracellular signals. The T3 (Leu4) structure is detectable in all human peripheral T cells. Antibodies to T3 are mitogenic to resting T cells and block cytolytic activity in both Class I and Class II reactive human T cells (reviewed by Reinherz et al., 1983; Fitch et al., 1983). Activation by anti-T3 antibodies is accompanied by the release of lymphokines including IL-2 and gamma-INF. The T3 complex in the human system consists of two glycoproteins (20 kd and 25 kd) and one non-glycosylated 20 kd protein. Close association between TcR and T3 is suggested by the fact that these two complexes co-modulate. Also, immunoprecipitates obtained from extracts of radiolabelled cells with anti-T3 antibodies contain the alpha-beta heterodimer in addition to the T3 molecules. However, in order to precipitate the T3 structure with antibodies to the heterodimer, the complex had to be treated with a crosslinker (Allison et al., 1984). Dr. Trowbridge and his collaborators have recently isolated TcR subunits in association with T3 using bifunctional crosslinkers. From their studies, it is suggested that the beta chain of TcR and the 25 kd subunit of T3 are in close proximity (Brenner et al., 1985). Strong non-covalent interactions between these units could explain earlier observations showing that either anti-TcR or anti-T3 antibodies induce co-capping (Meuer et al., 1983b).

It is commonly assumed that in addition to TcR, other structures must participate in the transduction of environmental signals to the interior of T cells to initiate the cellular response. Identification of membrane and cytoplasmic components interacting with the receptor and analysis of the events that follow antigen/MHC binding will help to understand how T cells are "triggered". Concerning the function of T3 in the activation of T cells, it has been shown that monoclonal antibodies directed against T3 and TcR induce a rapid and sustained rise in cytosolic free calcium, suggesting that the TcR-T3 complex is a membrane potential-sensitive calcium channel (Oettgen et al., 1985). Similarly, it has been proposed that the non-glycosylated hydrophobic 20 kd subunit of T3 is a candidate for a Ca++ ionophore, and that "triggering" of the cells through the TcR-T3 complex by clonotypic antibodies results in a clonal T-cell proliferation through an IL-2 dependent autocrine pathway (Acuto et al., 1985). Whether the same scheme explains antigen-induced clonal T-cell proliferation remains to be determined. While most of the studies on the structure and function of T3 have been done on human T cells, Drs. Allison and Lanier (1985) have recently identified a T3-like structure in murine T cells.

Earlier, Dr. Reinherz and his colleagues developed a method to characterize individual T-cell clones in humans by in vivo expansion of these clones using IL-2 and alloantigen stimulation (Meuer et al., 1982b). They found that most CTL clones were derived from T8+ cells. A more detailed investigation of the subsets showed that T4 and T8 are involved in the recognition function, rather than in the effector mechanism (Meuer et al., 1983b). Although their exact function is still unknown, these cells may serve in "ancilliary" binding capacity for an invariant portion of MHC antigens, acting as stabilizing elements to facilitate cell-to-cell contact, thereby making lysis of target cells by CTLs possible (Acuto et al., 1985).

Recognition of foreign antigen by T cells is restricted by products of the MHC. This restriction is acquired by differentiating T cells under the influence of MHC antigens expressed in the thymus. The mechanism of this process is still unknown. The currently favored model suggests that precursor T cells are selected on the basis of their binding to MHC determinants expressed in the thymus. Whether the dual recognition of antigen/MHC by TcR requires physical association of the nominal antigen with self components or whether it involves two TcR molecules is still unknown. The remarkable coherence of different lines of investigation, as outlined above, leaves little doubt that the alpha-beta heterodimer, and perhaps the gamma chain, are involved in TcR function. However, the concurrence of these observations does not constitute definitive proof that the heterodimer is the sole antigen/MHC-binding TcR. Indeed, other groups have suggested the involvement of molecules that appear to be different from the ones considered so far. For example, Robert Cone (CA 40630), Nancy Ruddle (CA 16885, CA 29606) and their colleagues used a completely different approach and arrived at different conclusions. They obtained an mRNA preparation from hapten (ABA)-specific suppressor T hybridomas by precipitating nascent ABA-binding protein-containing polyribosomes using an antibody against the antigen-binding TcR. However, the translated product of this mRNA is not identical to the previously discussed heterodimer (Beaman et al., 1984). Similar antigen-binding T-cell-derived proteins have been detected

by John Marchalonis (1985). The characteristics of these molecules are suggestive of antigen-binding TcRs; however, their relationship to the molecules obtained by others will have to be clarified (Cone and Beaman, 1985).

Chromosomal Location of TcR Genes

Previous studies suggested that genes coding for TcR are closely linked to the Ig heavy chain locus on chromosome 12 or to the MHC locus on chromosome 17 of the mouse. Drs. Eisen, Tonegawa and their collaborators have now determined the chromosomal location of genes for murine TcR. The alpha and gamma genes were found to be on chromosomes 14 and 13 respectively (Kranz et al., 1985). Since the gene for the beta chain had been previously found to be located on chromosome 6 (Lee et al., 1984), it appears that all three murine TcR genes are located on different chromosomes, as are the different Ig and MHC multigene families.

The chromosomal location of the human beta gene has been recently determined by Dr. Reinherz and his collabortors to be on chromosome 7 (Barker et al., 1985). The same chromosome has been implicated in acute lymphocytic leukemia (Yunis, 1983), which points to the role of this locus in the neoplastic transformation of T cells. Similar results were obtained independently by Carlo Croce (CA 23568) and collaborators who found the beta gene on the same chromosome. It has been shown previously that the terminal 7q segment is a "hot spot" for chromosomal rearrangements in normal T cells. Since the human beta TcR gene is located in the 7q35 band, it is possible that this locus is part of a "fragile site" which may reflect genetic instability, generated by somatic rearrangements of TcR genes during T-cell differentiation (Isobe et al., 1985).

Dr. Croce and his colleagues used a human alpha chain-specific clone of TcR and mapped the gene on chromosome 14. This gene appears to be proximal to the Ig heavy chain locus in the 14q11-q12 region which is known to be involved in translocations detectable in T-cell leukemias and lymphomas. Therefore, these workers suggested that the TcR alpha chain locus participates in the activation of oncogenes, leading to T-cell neoplasia (Croce et al., 1985). Similar results were obtained independently by Carol Jones (CA 18734) and her colleagues (Jones et al., 1985).

Regarding the chromosomal location of TcR-associated molecules, Leonard Herzenberg (CA 04681), Dr. Croce and colleagues have cloned the gene for human T8 and assigned it to chromosome 2, proximal to the Ig kappa gene (Sukhatue et al., 1985; Bruns et al., 1985). Similar linkage in the mouse had been suggested earlier (Gottlieb, 1975). The significance and functional implications of the conserved T8-TcR linkage group will have to be determined. It is interesting to note that T8 appears to be a surface Ig-like protein: it contains two external domains, a hydrophobic transmembrane region and a cytoplasmic tail. More importantly, the N-terminal domain is homologous to the V region of Igs and TcRs and the second external domain is homologous to that of the Ig heavy chains (Sukhatue et al., 1985).

Specificity of TcR

The specificity of TcRs remains controversial. Earlier experiments with heterogenous populations of helper T cells and CTLs suggest that TcRs have a broader range of antigen-binding specificities than B-cell-derived antibodies. Given the same determinant, T-cell responses are considered to be less discriminatory of the structure and conformation of antigen than are antibodies. However, as was pointed out by Eli Sercarz (CA 24442) and his collaborators, it is possible that earlier results which indicated less stringent specificities for TcR were experimental artifacts, caused by the extensive heterogeneity of T cells in the mixed populations (Shastri et al., 1984). The same group analyzed the rearrangement of the beta chain in functional T cells. The clone they studied was specific for the protein antigen egg white lysozyme. Interestingly, the same functional V (beta) gene segment was found to be expressed in a different clone, specific for cytochrome C, a non-crossreactive protein. Thus, no simple correlation has been demonstrated so far between individual V regions of TcR and antigen specificity or MHC restriction (Goverman et al., 1985). It is hoped that the use of cloned T-cell lines, T-cell hybrids and cloned TcR will now allow the definition of antigen-TcR interactions at the molecular level.

The role of MHC determinants in the cytolytic process is still unknown. Drs. Tonegawa, Eisen and their collaborators asked the question whether MHC products are required only for target cell recognition, or also for the lysis of these cells by CTL. They used TcR-specific monoclonal antibody to see whether the antibody can substitute for the natural ligand on the target cell in the cytolytic reaction, and if so, whether Class I MHC molecules are necessary for cell lysis. They found that all cells treated with the anti-TcR monoclonal antibodies were lysed by the specific CTL and not by other CTL clones (Kranz et al., 1984b). Therefore, it appears unlikely that Class I MHC molecules on the surface of target cells are directly involved in the cytolytic process. Similar findings were reported by Lancki and Fitch (1984).

Clinical Significance of TcR

The experiments discussed in the last section suggested a useful practical application of TcR-specific antibodies, namely to guide and focus T cells onto the target cells. The feasibility of this principle was examined by Dr. Bevan and colleagues who synthesized hetero-conjugates of monoclonal antibodies in which one of the two binding sites was specific for an allotypic determinant of TcR, the other was directed against a cellular target antigen. They found that such hybrid antibodies could, indeed, form bridges between CTLs and target cells and focus T cells to act specifically on the target (Staerz et al., 1985). This novel technology has therapeutic potential for the selective elimination of tumor cells and cells infected with viruses.

General failure of immune regulation and increased activities of suppressor T cells have been shown to contribute to the development of several forms of malignancies, as well as to AIDS. For instance, anti-T3 antibodies activate normal T cells, but not those obtained from AIDS patients (Acuto et al., 1985).

Identification of TcR and its associated structures is expected to contribute to our understanding of tumor immunology as well as to the diagnosis and therapy of neoplasia. Analysis of the rearrangements of the beta gene of TcR from twelve T-cell tumors indicated that patterns of gene rearrangement are useful markers to detect monoclonal T-cell tumors (Flug et al., 1985). The TcR beta gene was found to rearrange in all investigated T-cell acute lymphoblastic leukemia lines. In contrast, no rearrangement was found in DNA obtained from tumor cells of acute myeloblastic leukemia and of non-leukemic patients (Minden et al., 1985). These data suggest that either there is a limited variation of possible gene rearrangements or there is an association between the development of leukemias and patterns of TcR beta gene rearrangements. Thus, assessment of TcR gene rearrangement could be a valuable tool in the diagnosis of leukemias.

Anti-clonotypic monoclonal antibodies, specific for malfunctioning effector and regulatory T cells could provide a selective therapeutic strategy for diseases like multiple sclerosis, dermatomyosititis and rheumatoid arthritis (Reinherz et al., 1981). Tumors from patients with acute lymphoblastic lymphoma, chronic T-cell lymphatic leukemia, adult T-cell leukemia, Sezary Syndrome and mycosis fungoides are made up of mature, receptor-positive transformed T cells. Anti-clonotypic reagents and "immunotoxins" may become therapeutically useful in the control and elimination of these T-cell malignancies. In addition to these long-term goals, T-cell specific immunotoxins and other targeted drugs are being used for the selective in vitro elimination of residual leukemic cells in bone marrow for autologous transplantation. Preliminary trials have been reported by the Schlossman group using monoclonal antibodies and complement for purging autologous bone marrow prior to transplantation (Ritz et al., 1982). John Leonard (CA 35692) and his colleagues have recently coupled ricin to T-cell specific (allo-reactive) antibodies and showed that target T cells can be selectively removed by using such immunotoxins without excessively damaging normal cells (Leonard et al., 1985).

THE IMMUNOLOGIC FUNCTION OF SKIN

The skin, the largest organ of the body, has long been considered to be the first line of defense against pathogens, but only as a passive, physical barrier against infection. Recently, its role as an active component of the immune system has begun to be appreciated. It has been known for some time that the development of a T-lymphocyte response to antigens requires accessory cells to present antigens, and that this interaction between accessory cells and the responding cells is restricted by major histocompatibility complex (MHC) antigen recognition. Most studies have focused on the macrophage as the critical accessory cell to present antigen in this immune response. Other cell types, such as the Langerhans cells of the skin, have now been demonstrated to have the capacity to present antigens to T lymphocytes. The role of the skin in the immune response has recently been reviewed by Richard Edelson (CA 20499; Edelson and Fink, 1985).

T-Cell Maturation

Dr. Edelson's studies of the role of the epidermis in T-cell development evolved from his longstanding research interest in cutaneous T-cell lymphoma (CTCL). The most distinctive biological feature of the malignant T cells in this disease is their initial affinity for skin. His earlier finding that CTCL is a malignancy of helper T cells which interact with epidermal cells led to studies to determine if the skin, like the thymus, might be a site where certain types of T cells undergo maturation. Immature lymphocytes from the bone marrow migrate to the thymus where they mature to become cells that are identifiable as T lymphocytes. Several observations have suggested that the skin might have functions analogous to those of the thymus. Electron microscopy had indicated a striking similarity between epidermal keratinocytes and thymic epithelial cells, shown to have distinctive granular structures similar to those seen in keratinocytes. The basal layer of keratinocytes in skin have been shown to contain thymopoietin-like thymotrophic hormones (Chu et al., 1983). In addition, nude mice, which have long been used by immunologists because they congenitally lack a thymus gland and therefore fail to develop normal functional T cells, are named for their lack of mature hair, the major epidermal appendage. It has never been possible to separate the genes responsible for the absence of the thymus from the genes responsible for the absence of mature body hair.

Barton Haynes (CA 28936) and colleagues have obtained more evidence of similarities between the epithelial cells of the thymus and those of the skin. They have found distinctive cell surface antigens on human thymic epithelium which are recognized by a panel of monoclonal antibodies. Antibody TE-4 defines a cell surface antigen on endocrine thymic epithelial cells which are also positive for antigens recognized by monoclonal antibody A2B5 and anti-p19. Reactivity of TE-4 antibodies with a variety of normal tissues and cell types was determined using indirect immunofluorescence. TE-4 was shown to react only with thymic epithelium and, interestingly, with the basal layer of squamous epithelium in skin, esophagus, tonsil and conjunctiva. Experiments have demonstrated that the TE-4+ endocrine epithelium expresses MHC (Ia and HLA) antigens, and also contains thymosin-alpha-1 and keratin, indicating that this subset of thymic epithelial cells is a prime candidate for a cell type of the human thymic microenvironment that, in addition to thymic macrophages, may participate in conferring MHC restriction to maturing T lymphocytes (Haynes et al., 1984b). Long term in vitro cultures of human thymic tissue have been established and phenotypically characterized using monoclonal antibodies which define distinct components of the thymic microenvironment (McFarland et al., 1984; Haynes 1985a,b). The epithelial component of the thymus, which is defined by monoclonal antibodies TE-3, TE-4 and monoclonal antibodies against keratin, has been isolated from the mesodermal component which is defined by antibody TE-7 and maintained separately in long term cultures. The epithelial cells have been subcultured repeatedly, and their in vitro phenotype was compared to that of cultured human epidermal cells. A subpopulation of cultured thymic epithelial cells, along with the subpopulation of cultured epidermal cells, expressed antigens TE-8 and TE-15, characteristic of late stages of keratinized epithelial cell differentiation.

In further studies of T-cell maturation, Dr. Haynes and colleagues have found that monoclonal antibodies which react with Hassell's bodies (HB), epithelial swirls in the human thymic medulla thought to be derived from endocrine medullary thymic epithelium, identify HB as antigenically distinct regions of endocrine thymic epithelium. These anti-HB monoclonal antibodies also selectively react with epidermal keratinocytes in the terminal stages of maturation (Lobach et al., 1985). Drs. Edelson, Haynes and colleagues are attempting to establish a method to separate different keratinocyte subpopulations in the epidermis. The murine monoclonal antibody 4F2 was generated by immunizing mice with a human T-cell line, and recognizes the polypeptide portion of the heavy chain of a 120 kd cell surface glycoprotein detected on peripheral blood monocytes, on a subset of activated T cells, on in vitro colony-forming bone marrow cells and on a number of established lymphoid cell lines. This monoclonal antibody has now been demonstrated to react with a membrane antigen present on basal keratinocytes and will provide a useful probe for the isolation of this subpopulation, facilitating further study of both the normal biology and pathology of the epidermis (Patterson et al., 1984). Thus, the finding of distinctive marker molecules on the outer membrane of the thymic epithelial cells secreting thymic hormones, and on the surface of keratinocytes from basal layer of human epidermis which were shown to produce a substance closely resembling the thymic hormone thymopoietin, provides further evidence that these skin cells might be immunologically functional.

Antigen-Presenting Cells

In the past few years, our understanding of the role of antigen-presenting accessory cells in the induction of an immune response has increased greatly. It has become evident that a growing number of diverse cell types besides macrophages and monocytes can express Ia molecules and have antigen-presenting capabilities. In fact, the capacity of other cell types to act as accessory cells, because of their unique tissue or organ distribution, may be more important than that of macrophages in certain in vivo situations. Recently, it became evident that several groups of dendritic cells, including Langerhans cells (LC), interdigitating dendritic cells in lymph nodes, follicular dendritic cells, and lymphoid dendritic cells should be regarded as distinct from ordinary macrophages. Although some of these cells share features in common with macrophages, they differ in their shape, location and the presence of certain surface antigens. The phenotypic differences between dendritic cells and macrophages have been reviewed by Ralph Steinman (CA 30198) and colleagues (Van Voorhis et al., 1983). These investigators have demonstrated that dendritic cells are critical accessory cells for thymus-dependent antibody responses in man and in mouse (Inaba et al., 1983). Although dendritic cells and macrophages are frequently grouped together and not distinguished, these cells are leukocytes with different functions and phenotypes. Both lack lymphocyte differentiation markers, but express Class I and II products of the MHC. While dendritic cells, like macrophages, can sometimes be enriched by adherence to glass or plastic, there are many instances where they are non-adherent. The availability of specific monoclonal antibodies is now making it possible to measure the total accessory activity that is attributable to each cell type.

OKT6 cell surface antigen has been shown to be present on LC and on some dendritic cells in the paracortex, as well as on 70% of thymocytes, but not on monocytes. Drs. Timothy Springer (CA 31799), G. Jeanette Thorbecke (CA 14462) and associates have studied the tissue distribution of murine macrophage antigens to determine whether distinct subsets could be found, and whether these antigens would also be present on dendritic cells. The macrophage cell surface membrane antigens Mac-1, Mac-2, and Mac-3 are identified by monoclonal antibodies. Comparison of various dendritic cells and macrophages indicates that the Mac-1,2,3 phenotypes divide the cells into three categories that have other correlates in addition to these antigens. The Mac-1+,2+,3+ phenotype is limited to macrophages. The Mac-1-,2+,3+ phenotype includes LC, interdigitating dendritic and thymic dendritic cells. These cells have all been shown to be Ia-positive, are only minimally phagocytic, and have interactions with T cells. Kupffer cells are also Mac-1-,2+,3+ but can be highly phagocytic. Thus, they appear to have properties intermediate between macrophages and the other dendritic cells of this phenotype. The third phenotype Mac-1-,2-,3- is found on follicular dendritic cells; therefore, these cells differ from the other dendritic cells. The Mac-1,2,3 phenotype for lymphoid dendritic cells is not yet known but other surface properties make them much different from other dendritic cells (Flotte et al., 1983).

These investigators have used monoclonal antibodies to macrophage antigens, along with monoclonal antibodies to Ia antigen, Fc-fragment receptor, and the common leukocyte antigen (CLA) to compare the cell surface antigens of these cells with those of interdigitating and follicular dendritic cells and of macrophages in lymphoid tissues. LC of the epidermis were originally identified by their dendritic morphology and staining characteristics, and only recently have been found to be the antigen-presenting cells (APC) of the skin. They are Ia antigen-positive and appear to mediate the induction of contact sensitivity in vivo and the induction of antigen-specific T lymphocyte responses in vitro. These findings raise the question of the relationship of LC to APC in other tissues. LC, like macrophages, are derived from the bone marrow but the relationship of their precursors is unknown. Drs. Springer, Thorbecke and colleagues have demonstrated that LC bear the CLA antigen, which is identical to the Ly-5 antigen of the mouse, common to all leukocytes and found on hematopoietic stem cells but not in non-hematopoietic tissues. By studying epidermal cell suspensions highly enriched for LC, they have been able to demonstrate the presence Mac-2 and Mac-3 on LC as well as in keratinocytes (Haines et al., 1983).

Cell Interactions

While previous evidence had indicated that keratinocytes in culture are able, in the absence of LC, to induce the expression of a T-cell marker, and that they contain a molecule resembling the thymic hormone thymopoietin, the question remained whether the LC function alone or require a contribution from the keratinocytes.

Although LC are known to play an important role in initiating an immune response to antigens introduced through the skin, the mechanisms that regulate the movement of LC precursors into the epidermis, and antigen-bearing LC from the skin to draining lymph nodes, have not been identified. It is known that within the epidermis the keratinocytes can be induced to express Ia antigen and may function to direct the movement of lymphoid cells into the skin. Drs. Daynes (CA 22126, CA 25917), Roberts (CA 34302) and colleagues have reported that keratinocytes were induced to express Ia in rat and allogeneic mouse skin that was grafted onto athymic nude mice (Daynes et al., 1983; Krueger et al., 1983). This process was paralleled by the infiltration of host LC into the epidermis of the graft, suggesting a cause-and-effect relationship between these two events. More recent studies demonstrated that the keratinocytes of nude mice are induced to express Ia without any observable pathologic changes in the skin following the injection of serum (syngeneic or xenogeneic) or lymphoid cells (semi-syngeneic) from normal animals. A direct correlation between the ability of donor LC precursors to enter the epidermis, and the induceable expression of Ia by the host keratinocytes, was established in nude mice that received an adoptive transfer of lymphoid cells from either normal, semi-syngeneic or allogeneic nude donors (Roberts et al., 1985). While Ia-positive keratinocytes have been observed in individuals with skin diseases, in conditions where lymphoid cell infiltration into the skin occurs, inducing keratinocytes to express Class II MHC molecules (Ia) without associated pathologic changes suggests that the expression of Ia antigens by these cells may be part of a normal physiologic or immunologic response. The experimental evidence that keratinocytes actually synthesize the Ia that they express on their cell surface is consistent with this conclusion. Keratinocyte expression of Ia appears to facilitate the movement of LC precursors into the epidermis, but may also influence the movement of other immunologically functional cells into the skin. For example, Drs. Roberts and Daynes have demonstrated that delayed-type hypersensitivity responses in nude mice, whose keratinocytes were induced to express Ia by prior injection of normal mouse serum, were much greater than those observed in animals where Ia expression was not previously induced (Roberts et al., 1984; Daynes et al., 1985b). These findings indicate that once keratinocytes have been induced to express Ia, they can enhance the LC presentation of antigen to T cells.

Effect of Ultraviolet Radiation

It has been known for some time that that exposure of animals to ultraviolet radiation (UVR) can result in dramatic alterations in their immune response. Loss of ability to be contact sensitized to skin-reactive chemicals applied to UVR-exposed surfaces, and enhanced susceptibility to tumors induced by UVR, represent two well-documented effects of such exposure. It has been shown that LC are functionally inactivated by UVR. Dr. Daynes and colleagues have investigated the relationship between the UVR-mediated loss of contact hypersensitivity responsiveness and the APC function of LC following *in vivo* exposure of animals to UVR. The *in vivo* loss was found to be both time-dependent and dose-dependent, while the loss of epidermal APC function following

UVR exposure of dissociated epidermal cells or skin was immediate and dosage-dependent. These studies provide a possible explanation for apparent differences in sensitivity of LC to UVR which are observed when in vitro or in vivo assays are employed (Gurish et al., 1983).

Another type of immunologically active epidermal cell has been recently identified by Richard Granstein, Mark Greene (CA 14723) and colleagues. They exposed suspensions of mouse epidermal cells to UVR, thereby depleting them of functional LC. In the depleted suspensions, however, they could detect another type of dendritic APC which has come to be called the "Granstein cell." This cell is more resistant to UVR than the LC and has the tendency to interact with suppressor T cells, rather than helper T cells (Granstein et al., 1984a). Their data demonstrate that the induction of suppression after UVR treatment of epidermal cells is an active process requiring the presence of a UVR-resistant I-J+ epidermal APC. Discovery of the role of this cell in suppressor cell induction may help explain the development of tumor-related T suppressor cells. These investigators have hypothesized that UVR exposure of skin produces two damaging effects: 1) it causes the expression of certain UVR tumor-associated antigens by target cells through unknown processes and, 2) it also abrogates the ability of the skin to generate effector immune responses, presumably by diminishing the activity of Ia+ LC, and possibly also by affecting release of epidermal cell-derived thymocyte activating factor (ETAF), an entity biochemically and functionally very similar, if not identical, to interleukin-1 (IL-1). As a consequence, the UVR tumor-associated antigens are then "presented" predominantly by the UVR-resistant I-J+ Granstein cells to lymphocytes, resulting in the appearance of suppressor T cells. Such presentation and suppressor T cell activation could occur locally or, alternatively, the I-J+ APC may migrate to lymph nodes or spleen to induce suppression.

Dr. Greene, along with Carl Waltenbaugh (CA 34109) and colleagues, has demonstrated immunologic inhibition of UVR-induced tumor suppressor cell activity (Granstein et al., 1984b). Long-term exposure of mice to UVR resulted in the formation of suppressor T cells that recognize UVR-induced regressor skin cancers as a class, before the appearance of overt tumors. These investigators have demonstrated that the in vivo administration of monoclonal antibodies to the cell surface product of the I-J subregion of the MHC, or low doses of cyclophosphamide, inhibited the development of activity of these cells. These findings indicate that cells expressing the I-J determinant are important in regulating the host response prior to the overt development of UVR-induced skin cancers, and suggest novel therapeutic approaches to malignancies or other diseases involving suppressor T cells in their pathogenesis. Dr. Greene and colleagues have extended these studies to document the effect of UVR on splenic APC and have established that the subset of APC involved in the activation of suppression from the spleen or skin are UVR radiation-resistant and are adherent to plastic surfaces (Granstein and Greene, 1985). It is known that large doses of UVR cause systemic suppression of the ability to sensitize mice to haptens (antigens) and a systemic loss of functional Ia+ APC. While the mechanism of these effects is not known, one hypothesis is that APC are irradiated

in the microvasculature of the skin in situ prior to circulating and lodging in the spleen and elsewhere. If this hypothesis is correct, the in vitro UVR resistance of the I-J-bearing APC would be relevant to the UVR effects seen in vivo. These investigators speculate that UVR may inactivate Ia-bearing APC and cause the expression of certain UVR tumor-associated antigens by target cells in the skin through unknown processes. Then UVR-resistant APC can present certain of these tumor-associated antigens for suppressor cell activation. The sets of APC in the skin, therefore, may be crucial in determining the balance between immunologic responsiveness and suppression.

Drs. Daynes, Roberts and colleagues are continuing their studies on the cause-and-effect relationship between the acquisition of tumor susceptibility and the presence of T suppressor cells in the secondary lymphoid organs of UVR-exposed animals. For these studies they have chosen to analyze a more controllable system than tumor susceptibility. In UVR-exposed animals, contact hypersensitivity responses to skin-reactive chemicals are markedly affected, and reduced responses are paralleled by the presence of specific T suppressor cells, making this system similar to the tumor system. They have recently established that animals exposed to UVR become desensitized to the lymphokine IL-1, which appears to be mediated by a feedback regulation, as IL-1 itself plus other exogenous inducers of inflammation provide similar results. Desensitized animals, whether UVR-, lipopolysaccharide (LPS)- or IL-1-induced, each demonstrate a reduced capacity to respond to skin-reactive chemicals, and specific T suppressor cells are present within the spleens of these animals. Their results indicate that both UVR- and LPS-desensitized animals, treated with cyclophosphamide or anti-I-J antibodies to inhibit suppressor cell generation, remain hyporesponsive to contact hypersensitivity (Gahring et al., 1985). These investigators have demonstrated that UVR enhances the release by keratinocytes of ETAF, the hormone-like molecule that is similar or identical to IL-1 (Gahring et al., 1984). There is currently a controversy concerning whether UVR exposure of keratinocytes (or macrophages) results in increase, decrease or no change in the rate of ETAF/IL-1 secretion. Drs. Daynes, Roberts and colleagues have demonstrated that UVR exposure of animals results in the detection of circulating ETAF/IL-1 levels one to three days post-exposure, plus a marked increase in a variety of known ETAF/IL-1-induced effects. Furthermore, animals subjected to continued daily exposures of UVR lose their enhanced plasma levels of acute phase reactants by seven days into the treatment protocol, a situation which they have termed "UVR-desensitization" and appears analagous to a condition which can be produced by chronic endotoxin administration, termed "endotoxin tolerance." According to these investigators, the inability of UVR-exposed animals to respond to contact sensitization in a positive manner, and the induction of specific suppression as the dominant response observed, is in some way associated with the desensitization process and is therefore linked to IL-1. Confirmation of a definitive involvement of IL-1 in this immunoregulatory role must await the availability of sufficient quantitites of purified ETAF/IL-1 to conduct the appropriate in vivo experiments.

Dr. Daynes and co-workers have also presented data supporting the hypothesis that ETAF/IL-1 is involved in the enhancement of circulating lymphocyte sequestration to peripheral lymph nodes of UVR-exposed animals (Daynes et al., 1985b). The finding that UVR-induced desensitization took place in spite of demonstrable serum levels of ETAF/IL-1 suggests that desensitization is not caused by an inhibition of ETAF/IL-1 synthesis, but rather may result from inability of target cells to recognize or respond to this endogenous mediator, or to unavailability of serum-associated ETAF/IL-1 for the appropriate targets. The definitive studies in this area also must await the isolation and purification of high specific activity ETAF/IL-1.

These investigators have extended this research to follow-up their observation that the decrease in splenic APC function which follows short term exposure of mice to UVR is paralleled by an increase in APC function in the regional lymph nodes draining the irradiated site. They have found that UVR exposure resulted in a dramatic and long-lasting increase in the tropism of circulating lymphoid cells for peripheral lymph nodes. Termination of UVR exposure did not result in the reversal of this phenomenon. Since an increase in lymphocyte migration into the lymph nodes of UVR-exposed mice was apparent within two hours of infusion of radiolabelled cells, they concluded that the homing assay data reflected an increased binding of circulating lymphocytes to high endothelial venules (HEV) within the lymph nodes of irradiated animals. Histologic analysis of skin from UVR-exposed mice established that the dermal microvasculature had expanded in terms of size and number of vessels, a combination that also does not completely reverse after the termination of treatments. In spite of the increase in dermal microvasculature, very few inflammatory cells were detected in the irradiated skin site. The investigators concluded that the enhanced traffic of lymphocytes into peripheral lymph nodes of UVR-exposed mice occurs primarily via lymphocyte-HEV interactions, rather than afferent drainage of the irradiated skin (Spangrude et al., 1983).

The continued exposure of lymphocytes to foreign structures present on the surface of UV-irradiated tissue, before the emergence of overt tumors in the tissue, would insure maintenance of suppression and aid in the progression of a tumor without interference from the host immune apparatus once an active state of tolerance is established. Selective lymphocyte migration is an important factor in determining the *in vivo* distribution of functionally distinct lymphocyte subpopulations. Dr. Daynes with Barbara Araneo (CA 38349) and colleagues are continuing these studies using pertussis toxin (PT), a known inhibitor of lymphoid cell migration *in vivo*, to demonstrate that the blockade of lymphocyte extravasation potential mediates inhibition of certain cell-mediated immune responses *in vivo* (Spangrude et al., 1985). Their results showed that the homing potential of primed cells, treated *in vitro* with PT, is accompanied by an inhibition of antigen-specific contact hypersensitivity following adoptive transfer into naive mice. This suggests that the process of lymphocyte extravasation into non-lymphoid tissue sites, such as the skin, shares fundamental similarities to the homing of circulating lymphocytes to lymph nodes. Further, the inhibition of contact sensitivity observed following the intravenous adoptive transfer of toxin-treated antigen-primed cells could be circumvented by transferring the PT-treated cells

directly into a tissue site with the relevant antigen. In contrast, no inhibition in the number of antibody-forming cells present within the spleen was observed following an adoptive transfer of PT-treated sheep red blood cell-primed lymphocytes. Thus, the inhibitory effect of PT exposure was established to be a direct result of the toxin-mediated alteration of cellular migration, since PT inhibits the entrance of lymphocytes into specific tissue sites without inhibiting other cellular function. Since lymphocytes which had been pretreated with PT exhibit normal in vitro responses, these studies indicate that lymphocyte extravasation is a critical component in the development of cell-mediated immune responses in vivo.

Considering the emerging appreciation of the role of the skin in the systemic immune response, it is noteworthy that Fred Valentine (CA 34976) and colleagues have proposed that the causative agent of Acquired Immune Deficiency Syndrome (AIDS) infects LC and other dendritic cells of the skin. Kaposi's Sarcoma (KS) is a multi-focal tumor believed to be of endothelial cell origin. As endothelial cells are closely related to dendritic cells, these investigators have speculated that the high incidence of KS in AIDS is related to damage done to LC and endothelial cells. Alternatively, deficient LC function may prevent adequate presentation of KS-specific tumor antigens, leading to tolerance of these antigens through the induction of suppressor T lymphocytes and consequent widespread growth of KS (Belsito et al., 1984). This subject will be discussed in further detail in the following section on AIDS.

The concept of lymphocyte traffic through normal and chronically irradiated skin is not a new one. It has been proposed that the specialized network of structures in the skin can be defined as comprising the skin-associated lymphoid tissue (SALT), suggesting there might exist a subpopulation of lymphocytes that recirculate predominantly, if not exclusively, from the peripheral blood to the skin and to the lymph nodes that drain the skin. Recirculation of lymphocytes plays a major role in the in vivo function of the immune system, and thus, homeostasis of the host organism. In the case of UVR, the chronic inflammation and accompanying increase in lymphocyte homing may provide an opportunity for a prolonged interaction between the immune system and weakly antigenic neo-antigens that arise during the course of UV irradiation. The immunobiology of UVR carcinogenesis has recently been reviewed (Daynes et al., 1985a) and research is continuing to better understand why suppression emerges as the dominant response after this interaction.

ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS)

Several grants have been funded within the past three years specifically for the study of AIDS. In addition, other funded research grants have supported studies of AIDS, or related to AIDS, within the context of a broader overall scope. This report will highlight some of the AIDS research supported by the Immunology Program, Division of Cancer Biology and Diagnosis and is not intended to be a comprehensive summary of the ongoing research on immunologic

aspects of AIDS. Much of the basic research on the immunology of AIDS is included in grants supported by the Divisions of Cancer Treatment and Cancer Etiology; therefore, the results of research supported by those grants are not covered in this report. The range of immune defects in AIDS was evaluated by the Working Group on AIDS of the Clinical Immunology Committee of the International Union of Immunologic Societies/World Health Organization, and a summary was recently published (Seligmann et al., 1984). The discovery of HTLV-III as the probable cause of AIDS has had a major impact on research directions, and investigators are constantly interpreting their experimental results within the currently-accepted hypothesis that HTLV-III is the etiologic agent of AIDS.

Evan Hersh (CA 34673) and colleagues have continued to study a large group of patients who were either symptom-free high-risk subjects, subjects with AIDS-Related Complex (ARC) or subjects with AIDS. They have now entered a total of 470 patients into this study. The symptom-free patients have a defined immunologic abnormality, and 10 of the 20 immunologic parameters are abnormal in this group (Newell et al., 1985). The abnormality worsens as the disease progresses from symptom-free to ARC, and then to AIDS (Hersh et al., 1984, 1985b). Thymosin-alpha-1 is equally elevated in all categories of disease. Serum alpha-interferon (IFN) is elevated only in those patients with AIDS, and predominantly in those with opportunistic infection. The most important immunologic prognostic variables appear to be low absolute numbers of T4+ (T helper cells) and an inverted T4:T8 (T helper:T suppressor) cell ratio. Studies of interleukin-2 (IL-2) production and response have shown that IL-2 production in ARC patients is relatively normal, but is moderately depressed in AIDS patients. IL-2 response by mitogen-stimulated lymphocytes of both ARC and AIDS patients is poor (Reuben et al., 1985). In studies of the in vitro leukocyte response of AIDS and ARC patients to herpes simplex viruses (HSV) Type I and II and to cytomegalovirus (CMV), lymphocyte proliferation, natural killer (NK) cell activation and IFN production were markedly depressed, and this depression was independent of the stage of disease. The addition of IL-2 in vitro partially corrected this abnormality (Hersh et al., 1985a). In studies of expression of activation antigens on mitogen-stimulated T lymphocytes from AIDS patients, marked reduction in the expression of IL-2 receptor was noted. This finding may explain the deficient IL-2 response in these patients (Munn et al., 1985). These investigators have defined the immunologic parameters in AIDS, and are now applying this information to the development of therapeutic approaches using immunorestorative agents.

In continuing studies of the role of IFN in AIDS, Olivia Preble (CA 34994) and colleagues have confirmed that almost all patients with AIDS and opportunistic infections have endogenous circulating acid-labile alpha-IFN, whereas only 40-60% of AIDS patients with Kaposi's Sarcoma (KS) alone have detectable acid-labile IFN in their serum. Since all of the AIDS patients studied had antibody to HTLV-III, circulating alpha-IFN did not correlate with the presence of anti-HTLV-III antibody. The reason for this difference is unknown, but additional follow-up of homosexual men has confirmed previous studies indicating that development of circulating acid-labile alpha-IFN is a prognostic indicator in members of high-risk groups (Preble et al., 1984). Dr. Preble and colleagues have continued to monitor 2'-5' oligoadenylate

(2-5A) synthetase, an enzyme specifically induced by IFN, in peripheral blood mononuclear cells (PBMC) of patients with KS before, during and after IFN therapy. Compared to PBMC from healthy heterosexual controls, cells from both healthy homosexual men and AIDS patients were markedly deficient in their ability to respond to alpha-IFN in vitro with increased 2-5A synthetase activity. This inability of cells to respond biochemically to IFN also occurred in AIDS patients in vivo. Only 10 of the 28 AIDS patients treated with alpha-IFN developed increased synthetase activity despite high titers of circulating IFN and lack of detectable anti-IFN antibodies during therapy; four patients actually had significant decreases in this IFN-induced enzyme during alpha-IFN therapy. Exposure to IFN down-regulates expression of IFN receptors on the cell surface, which may account in part for decreased synthetase induction in vitro and in vivo in some of the AIDS patients in this study (Preble et al., 1985). It was not possible to predict clinical response to therapy on the basis of either in vitro or in vivo increases in 2-5A synthetase, although each patient with a significant decrease in enzyme activity during the first month of therapy had progressive disease while receiving alpha-IFN. Endogenous circulating alpha-IFN prior to therapy, however, was predictive of progressive KS during IFN therapy (Gelmann et al., 1985).

Alan Winkelstein (CA 24429) and colleagues have studied the clonal growth of human T-lymphocyte colonies in semi-solid media, to evaluate the interaction of factors controlling normal lymphopoiesis, and have found that the proliferative capacity of lymphocytes from AIDS patients is profoundly depressed. A less pronounced reduction was found in patients with ARC (Winkelstein et al., 1985). The T-lymphocyte colony assay proved to be a more sensitive indicator of immune aberrations then the standard assays of proliferative responses to non-specific mitogens. In a majority of ARC patients, the proliferative defects were corrected by addition of IL-2. By contrast, only a modest increase in response was observed with lymphocytes from AIDS patients. Cells from hemophiliacs with unexplained lymphadenopathy, a possible equivalent of the ARC syndrome, behaved similarly to cells from ARC patients (Ragni et al., 1984).

Intravenous (I.V.) drug abusers are at high risk for the development of AIDS. Stanley Schwartz (CA 35922) and colleagues have examined the peripheral blood lymphocytes of a group of male patients admitted to the hospital for infectious complications of I.V. drug abuse. These patients demonstrated significantly decreased levels of NK and antibody-dependent cell-mediated cytoxicity (ADCC) activities compared to appropriate healthy controls. Although the lectin phytohemagglutinin could considerably enhance the cytotoxicity of these patients' lymphocytes, activity was not completely restored to normal levels. Sera from I.V. drug abusers demonstrated a significant inhibitory effect on the NK and ADCC activities of normal allogeneic lymphocytes, even though these sera contained normal levels of circulating IFN. NK activity could be increased by IFN or IL-2 but could not be restored to normal levels (Nair et al., 1985).

John Fahey (CA 12800) and colleagues have verified the importance of making quantitative measurements of T4 (T helper) lymphocyte changes to distinguish AIDS from other immune disorders (Fahey et al., 1984). Infection

with CMV, Epstein-Barr Virus (EBV) and other agents can be associated with T8 (T suppressor/cytotoxic) cell increases in homosexually-active men, causing an abnormal subset ratio which does not have the same significance as an abnormal ratio caused by the low numbers of T helper cells associated with HTLV-III infection (Detels et al., 1984). Sexual partners of hemophiliacs with T-cell subset abnormalities have not acquired this abnormality (Kreiss et al., 1984). Alpha-IFN therapy of AIDS/KS was not associated with restoration of normal immune function even though some patients had complete or partial remission of KS (Groopman et al., 1984). Additional studies on the relevance of immunologic changes to prognosis in KS were carried out in 96 patients. The immunologic parameters that related to prognosis were the depressed T4 cell levels, depressed T4:T8 ratio, decreased proliferative response to mitogen and elevation of OKT10 antigen expression. Other immunologic parameters did not relate to prognosis (Afrasiabi et al., 1985). This work indicates that immunologic parameters have a prognostic significance that is independent of clinical parameters, e.g., fever, weight loss or night sweats. AIDS patients' monocytes had reduced ability to cooperate in antigen and mitogen stimulation of the immune system, thus adding to the defective immune response, secondary to lymphocyte alterations (Prince et al., 1985). Depressed IL-2 receptor (Tac) expression is regularly observed in AIDS lymphocytes, and depressed IL-2 production was less frequently observed in patients with AIDS and ARC (Prince et al., 1984). Evidence of lymphocytic immaturity, and possible activation, was obtained by detection of ecto-5'-nucleotidase deficiency in AIDS lymphocytes. This change was largely in the T8 lymphocyte subset, but also involved B cells (Salazar-Gonzales et al., 1985). These studies further support the importance of recognizing that AIDS represents a broad spectrum of clinical manifestations with a central underlying defect in the T4 subpopulation, along with many other immunologic abnormalities.

Roland Mertelsmann (CA 33873) and colleagues are continuing studies to define the molecular events which lead to IL-2 and IL-2 receptor gene expression in T lymphocytes from normal donors and from patients with congenital and acquired immune deficiencies, such as AIDS. A significant *in vitro* enhancement of defective immune responses by IL-2 has been documented, and the role of IL-2 in regulating immune function has been reviewed recently (Welte and Mertelsmann, 1985). These studies have led to clinical trials using IL-2 to treat patients with AIDS and with some lymphoid cancers. Some clinical improvements have been documented, but are difficult to attribute unequivocally to the IL-2 therapy (Mertelsmann and Welte, 1984). The recent cloning of the gene for IL-2, and the location of this gene on chromosome 4 by this group of investigators (Sykora et al., 1984) will facilitate research on the molecular basis of defects of IL-2 production and response in AIDS (Mertelsmann et al., 1984).

Barton Haynes (CA 28936) and colleagues, studying the T-cell leukemia virus from patients with adult T-cell leukemia, have developed a panel of monoclonal antibodies which react with human T-cell leukemia/lymphoma virus-I (HTLV-I): antibodies HTLV-6,7,8, and 9, which recognize the 24 kd internal core protein of HTLV-I (Palker et al., 1984), reacted only with HTLV-I-infected cells, and not with normal, neoplastic, mitogen-stimulated or other virus-infected cells. HTLV-p24 internal core protein was localized

at the cell surface of HTLV-I-infected T cells and is likely associated with the areas of budding virus particles. These monoclonal antibodies identified at least two different antigenic determinants on HTLV-I p24 that were also recognized by antibodies present in HTLV+ patients' sera. These antibodies also recognized cell surface determinants on T cells infected with HTLV-II, a type of HTLV isolated from a patient with a T-cell variant of hairy cell leukemia. Four additional monoclonal antibodies have been developed which bind to the 19 kd gag-encoded protein of HTLV. These antibodies, HTLV-2,3,4, and 12, unlike the anti-p24 monoclonal antibodies, bind only to the p19 of HTLV-I, and not to HTLV-II p19. Therefore, antibodies against the p19 and p24 can be used serologically to distinguish between HTLV-I- and HTLV-II-infected T cells (Haynes et al., 1984a). Since these viruses are related to HTLV-III, these monoclonal antibodies should prove useful to detect HTLV-III-infected cells and HTLV-III antigen or antibody in clinical samples, and will be important research tools to better understand the pathogenesis of AIDS.

Studies of HTLV-III as the etiologic agent of AIDS have indicated the tropism of this virus for the T4+ subset of T lymphocytes, suggesting that the depletion of the T helper cell type may be the primary immunologic defect in AIDS. It is still unclear if the entire T4+ subset of cells is affected, or if only a smaller subset of these cells is susceptible to HTLV-III infection. The broad range of clinical manifestations of AIDS has led to hypotheses that the primary immunologic defect may be due to infection of other immune cell types in conjunction with T4+ lymphocytes. Susan Zolla-Pazner (CA 15585) has presented data supporting the hypothesis that the etiologic agent of AIDS may infect both B and T cells, since infection of B cells by HTLV has been documented. There is marked polyclonal B-cell activation in AIDS, and B-cell abnormalities are amongst the earliest signs of AIDS and contribute significantly to its pathogenesis (El-Sadr et al., 1984). Dr. Zolla-Pazner has suggested that the etiologic agent of AIDS may be capable of infecting and activating B cells, and that this B-cell activation alters the homeostasis of the immune system, leading to stimulation of T suppressor cells, with subsequent suppression of cellular immune function (Zolla-Pazner, 1984). This hypothesis is supported by the findings that 1) patients with AIDS have elevated levels of immunoglobulin, reflecting the apparent polyclonal activation of B cells; 2) PBMC of AIDS patients have a reduced proliferative response to B-cell mitogen, consistent with the hypothesis that the B cells of AIDS patients are stimulated *in vivo* and cannot be further stimulated *in vitro*; 3) histologic abnormalities in the lymph nodes of AIDS patients are found primarily in the B rather in the T-cell zones of the lymphoid tissues; 4) in addition to KS, lymphoid tumors are the second most common malignancy seen in AIDS and are primarily of the B-cell type; 5) serum beta-2 microglobulin levels are elevated in AIDS patients. In addition, antibody titers to EBV, a B-cell tropic virus, are more profoundly elevated in AIDS patients than are antibody titers to other herpes viruses, such as CMV and HSV I and II, a finding which would also be expected if individuals seropositive for EBV were infected with another B-cell tropic agent.

Fred Valentine (CA 34976) has established several cell lines of B-cell lineage from small numbers of PBMC, without the addition of exogenous EBV, from patients with AIDS or ARC from several high-risk groups (Valentine

and Paolina, 1985). These cells are positive for Epstein-Barr nuclear antigen. Thus, the early detection of monoclonality and the establishment of lines from such small cell numbers suggest an increased frequency of cells "immortalized" in vivo by EBV. This may be important in the development of B-cell lymphomas in AIDS. The hypothesis that B cells may be the prime target cell of the AIDS virus could explain these observations, but until further research is done, this remains a controversial area.

Other candidates for the target cell underlying the profound immunologic dysfunction in AIDS are the antigen-presenting cells (APC). Drs. Valentine, Thorbecke and colleagues have investigated the possible role of a defect in APC in AIDS, by enumeration of Langerhans cells (LC), the epidermal APC. The evalution of these cells by staining for their characteristic markers, surface Ia antigen and surface ATPase activity indicated a significant reduction in the number of stained cells per square millimeter of body surface area in 24 patients with AIDS and either opportunistic infection or KS, as compared to appropriate controls. In addition, studies of six patients with ARC revealed significantly reduced numbers of LC. The reduction in Ia antigen was more pronounced than the reduction in ATPase activity. Given the known role of Ia expression in antigen presentation, these investigators have suggested that functional alterations in LC, and perhaps also in APC in tissues other than skin, may be involved in the pathogenesis of AIDS (Belsito et al., 1984). An alternative explanation is that polyclonal B-cell activation could cause the production of autoantibodies or immune complexes which interact with LC and block their surface staining characteristics. Whether such antibody could interfere with the ability of LC in the epidermis to function in presenting antigen to T cells requires further investigation. Any destructive effect or inhibitory influence on surface Ia expression of dendritic cells could result in the defective T4+ helper proliferation that is known to occur in AIDS. According to this hypothesis, the helper cell functional deficit would be an important step toward the ultimate immune deficiency, but not its primary cause. Although it is possible that AIDS is a disease of the APC system, this abnormality may be superimposed on an already impaired T4+ cell function, thus leading to an irreversible immunodeficiency. In addition, since dendritic cells are related to endothelial cells, and KS is thought to be a multifocal endothelial cell sarcoma, these investigators have speculated that the etiologic agent of AIDS affects both endothelial and dendritic cells. Alternatively, deficient LC function could interfere with the tumor-associated antigens of KS, thereby leading to tolerance of these antigens through induction of suppressor T cells, with consequent widespread growth by a process similar to that demonstrated for cutaneous tumors induced by UVR. If these hypotheses are correct, the administration of lymphokines known to stimulate Ia expression may be a reasonable approach to the correction of this defect in antigen presentation. Gamma-IFN, IL-1 and IL-2 may be appropriate candidates.

Several laboratories are continuing studies of the immunosuppressive effect of retrovirus infection. Noorbibi Day (CA 34103) and colleagues are investigating the mechanism by which feline leukemia virus (FeLV) causes neoplastic or non-neoplastic diseases in the infected cat, including the state of immunodeficiency characterized by decreased cellular and humoral immunity. They have demonstrated antiviral activity, characterized as a gamma-like IFN, in

supernatants from cultures of normal feline lymphocytes stimulated with Staphylococcus enterotoxin A. With the addition of inactivated FeLV, markedly less IFN was produced, which was not attributable to lowered lymphocyte viability or reduced mitogenic properties of the enterotoxin, but appeared to be a direct retroviral effect (Engelman et al., 1985). Gamma-IFN occupies a pivotal regulatory role in cellular immune responses, enhancing activity of macrophages, cytotoxic and natural killer cells, and the expression of IL-2 receptors on T cells. Therefore, deficient synthesis of gamma-IFN may play a role in the pathogenesis of immunodeficiency in FeLV-infected cats, a finding which may be related to the retroviral etiology and pathogenesis of AIDS.

The immunosuppressive property of retroviruses has been attributed to the structural envelope protein p15E, shown to have both immunosuppressive and anti-inflammatory activities which may contribute to the pathogenicity of this group of viruses. Murine and human neoplastic cells, not infected with retroviruses, have recently been found to contain p15E-like antigens. Ralph Snyderman (CA 29589) and George Cianciolo (CA 34671) have recently reviewed the literature and their own findings which indicate that factors produced by tumor cells, which depress macrophage-mediated functions, may be related to p15E (Snyderman and Cianciolo, 1984). An association of p15E expression with rapid cell division was suggested by the finding that mitogen stimulation of normal human PMBC induced the expression of p15E antigen (Cianciolo et al., 1984a). In addition, these investigators have identified sequence homology between a portion of the p15E envelope protein of murine and feline leukemia viruses and the p21E envelope protein of HTLV-I and II (Cianciolo et al., 1984b). To study the severe immunosuppression often associated with both human and animal retroviral infections, they synthesized a peptide of 17 amino acids (CKS-17) corresponding to the highly conserved regions of homology of p15E and p21. In a dose-dependent manner, CKS-17 coupled to bovine serum albumin inhibited murine IL-2-dependent and human mitogen-stimulated lymphocyte proliferation (Cianciolo et al., 1985). This synthetic peptide also inhibited the respiratory burst of human blood monocytes, an important component of the bactericidal and tumoricidal properties of these phagocytic cells (Harrell et al., 1985). These results indicate that this highly conserved region of the envelope proteins of retroviruses may be, at least in part, responsible for the immunosuppression often associated with these infections. The activity of this synthetic peptide provides an important new probe for investigation of the mechanism of this immunosuppression and may provide for the development of antibodies useful for the diagnosis and treatment of retroviral diseases.

Monoclonal antibody to p15E has been demonstrated to have biological activity against anti-inflammatory factors produced by bovine ocular squamous carcinoma cells (Nelson et al., 1985). Snyderman and Cianciolo (1984) have suggested that, whereas oncogene activation can induce neoplastic transformation, the expression of a p15E-like protein may allow transformed cells to escape immune destruction. The immunosuppressive activity of p15E could be important in promoting tumorigenesis in vivo if transformed cells acquire the ability to synthesize this product. In addition, the conservation of homology of immunosuppressive portions of p15E suggests that the envelope proteins of human lymphotrophic retroviruses have immunosuppressive activity similar to that of the envelope proteins of the retroviruses of other species, and may be significant in the pathogenesis of AIDS.

Richard Olsen (CA 31547) and colleagues have also demonstrated that UV-inactivated FeLV (FeLV-UV) and p15E retroviral proteins block the lymphokine-induced proliferation of the murine IL-2-dependent cell line CTLL-20. Suppression of CTLL-20 proliferation required only brief contact (6 hours) with FeLV-UV or with p15E, but was most efficient after prolonged (24 hour) contact with these agents. This suppression was reversible, and data suggest that FeLV does not block CTLL-20 proliferation by absorbing or inactivating IL-2 or by occluding IL-2 receptors, but rather that T lymphocytes develop an insensitivity to lymphokines after contact with FeLV-UV. This may be caused by a metabolic rather than a immunologic defect. Because lymphokines are requisite signals for T cell function, considerable immunosuppression would be associated with this acquired lymphokine insensitivity (Orosz et al., 1985).

Kent Weinhold (CA 33387) and colleagues had previously demonstrated that antibody against viral gp71 is effective therapeutically for high leukemic AKR mice if injected immediately after birth. No corresponding effect could be observed after inoculation later in life, when the endogenous virus burden is already high. However, if antibody treatment was supplemented by the injection of anti-p15E antibody, a therapeutic effect was observed even in older mice first treated at an age of two and one-half months. Those mice produced antibodies against viral surface proteins and appeared to be able to survive longer than the control mice. Thus anti-p15E antibody might be able to overcome retroviral-associated immunodeficiency, a finding which may have implications for the treatment of retrovirus-induced AIDS (Schwarz et al., 1984).

ADDITIONAL NOTEWORTHY FINDINGS

Several interesting observations have been reported recently which are worthy of mention in this report. Their implications have not yet been adequately investigated, and it is unclear at this time what their biologic, diagnostic or even therapeutic applications will be.

- Recently, studies have demonstrated that the metastatic properties of certain mouse tumors are correlated with the relative expression of Class I MHC antigens. Michael Feldman (CA 29139) and colleagues used MHC-gene transfection to restore expression of H-2K antigens in metastatic and non-metastatic subclones of a murine fibrosarcoma that lack their MHC-encoded H-2K antigens. De novo expression of H-2K reduced tumorigenicity and abolished the formation of metastases in syngeneic mice. Expression of H-2K may lead to effective recognition of disseminating tumor cells by the host immune system (Wallich et al., 1985).

- W. John Martin (CA 33693), John Minna and colleagues have described marked deficiencies of expression of HLA-A,B,C and beta-2 microglobulin on a panel of human small-cell lung cancer (SCLC) cell lines. In patients, SCLC exhibits rapid growth and early metastasis, suggesting

resistance to immune control. These HLA deficits contrast SCLC with human lung cancers of other histologic types, which were found to readily express Class I antigens. This difference in HLA expression may be related to differences in the clinical and molecular biologic behavior of these two categories of human lung cancer (Doyle et al., 1985).

- Mark Greene (CA 14723) and colleagues have found that exposure of neu oncogene-transformed NIH 3T3 cells to monoclonal antibodies reactive with the neu gene product p185 resulted in the rapid and reversible loss (down-modulation) of both cell surface and total cellular p185. Although not directly cytotoxic, monoclonal antibody treatment caused neu-transformed NIH 3T3 cells to revert to a non-transformed phenotype. This treatment had no effect on the anchorage-independent growth of NIH 3T3 cells that contained both the neu and the ras oncogenes, suggesting that the ras gene-encoded p21 molecule can replace the function of the neu gene-encoded p185 molecule (Drebin et al., 1985).

- The molecular mechanisms of target cell cytolysis by effector cells are still largely unknown. Earlier collaborative studies by Hudig (CA 28196), Redelman (CA 38396), Mendelsohn (CA 34077) and their collaborators suggested the involvement of serine-dependent endoproteinases in the cytolytic activity of NK cells (Hudig et al., 1981, 1984) and CTLs (Redelman and Hudig, 1980, 1983). Pasternack and Eisen (1985) have now demonstrated the presence of a novel serine esterase in CTLs. The activity of this 28 kd enzyme can be blocked by serine esterase inhibitors. Non-cytotoxic T and B cells had about 300-fold less esterase activity than CTL clones; moreover, in thymocytes, the esterase activity increased 20-50 fold after these cells had been stimulated in vitro to generate CTLs.

CONFERENCE SUPPORT

The Immunology Program provided funds for partial support of the following conferences in FY 1985:

"1985 Annual Symposium in Fundamental Cancer Research - Immunology and Cancer"
February 26-March 1, 1985 Texas

"Fourth HLA and H-2 Cloning Workshop"
June 30-July 2, 1985 California

"Gordon Conference on Immunochemistry and Immunobiology"
July 15-19, 1985 New Hampshire

FISCAL YEAR 1985

IMMUNOLOGY PROGRAM

SUMMARY OF GRANTS BY SUBCATEGORY

(Includes P01, R01, R23, R35, R43, U01, R13 Grants)

Dollars in Thousands

Subcategory	No. of Grants	Total Costs Awarded
Myeloma Proteins	12	$ 1,708
Cell Surface Antigens	45	6,847
Cell Surface Determinants of Lymphocytes & Macrophages	46	7,462
Humoral Factors Other Than Antibody	37	5,111
Tumor-Related Antibodies	15	1,727
Immunobiology of Sarcomas, Carcinomas & Melanomas	6	1,092
Host/Tumor Immunopathology	10	1,535
Effects of Disease on Immune Function	23	2,430
Immunotherapy: Mechanisms Rather Than Therapeutic Result	11	1,453
Lymphocytes	88	15,093
Monocytes & Macrophages	30	6,150
Malignancies of the Immune System (Lymphoma/Leukemia)	20	2,608
Immune Surveillance	30	3,518
Immunotherapy in Animal Models	8	1,024
Bone Marrow Transplantation	11	2,296
Conference Grants	3	24
	395	60,078

REFERENCES

Acuto, O., Fabbi, M., Bensussan, A., Milanese, C., Campen, T.J., Royer, H.D. and Reinherz, E.L. The Human T-Cell Receptor. J. Clin. Immunol., 5:141-157, 1985.

Acuto, O., Fabbi, M., Smart, J., Poole, C.B., Piotentis, J., Royer, H.D., Schlossman, S.F. and Reinherz, E.L. Purification and N-terminal Amino Acid Sequencing of the Beta Subunit of a Human T Cell Antigen Receptor. Proc. Natl. Acad. Sci., USA, 81:3851-3855, 1984.

Acuto, O., Hussey, R.E., Fitzgerald, K.A., Piotentis, J.P., Meuer, S.C., Schlossman, S.F. and Reinherz, E.L. The Human T Cell Receptor. Appearance in Ontogeny and Biochemical Relationship of the Alpha and Beta Subunits on IL-2 Dependent Clones and T Cell Tumors. Cell, 34:717-726, 1983.

Afrasiabi, R., Fahey, J.L., Taylor, J., Korns, E., Weaver, J. and Mitsuyasu, R. A Prognostically Significant Classification of Immune Changes in AIDS with Kaposi's Sarcoma. Blood, in press, 1985.

Allison, J.P. and Lanier, L.L. Identification of Antigen Receptor-Associated Structures on Murine T Cells. Nature, 314:107-109, 1985.

Allison, J.P., McIntyre, B.W. and Block, D. Tumor-Specific Antigen of Murine T-Lymphoma Defined with Monoclonal Antibody. J. Immunol., 129:2293-2302, 1982.

Allison, J.P., Ridge, L., Lund, J., Gross-Pelose, J., Lanier, L. and McIntyre, B.W. The Murine T-Cell Antigen Receptor and Associated Structures. Immunol. Rev., 81:145-160, 1984.

Barker, P.E., Ruddle, F.H., Royer, H.D., Acuto, O. and Reinherz, E.L. Chromosomal Location of Human T Cell Receptor Gene. Science, in press, 1985.

Beaman, K.D., Ruddle, N.H., Bothwell, A.L. and Cone, R.E. Messenger RNA for Antigen-Specific Binding Molecule from an Antigen-Specific T-Cell Hybrid. Proc. Natl. Acad. Sci., USA, 81:1524-1528, 1984.

Belsito, D.V., Sanchez, M.R., Baer, R.L., Valentine, F. and Thorbecke, G.J. Reduced Langerhans' Cell Ia Antigen and ATPase Activity in Patients with the Acquired Immunodeficiency Syndrome. N. Engl. J. Med., 310:1279-1282, 1984.

Bigler, R.D., Fisher, D.E., Wang, C.Y., Rinnoy-Van, E.A. and Kunkel, H.G. Idiotype-like Molecules on Cells of a Human T-Cell Leukemia. J. Exp. Med., 158:1001-1010, 1983.

Boon, W., Jayne, J., Palmer, E., Kappler, J. and Marrack, P. Rearrangement of T Cell Receptor Beta Chain Genes During T Cell Development. Proc. Natl. Acad. Sci., USA, 82:2925-2929, 1985.

Brenner, M.B., Trowbridge, G.S. and Stromimger, J.L. Cross-Linking of Human T Cell Receptor Proteins: Association between the T Cell Idiotype Beta Subunit and the T3 Glycoprotein Heavy Subunit. Cell, 46:183-190, 1985.

Bruns, G., Kavathas, P., Shiloh, J., Sakai, K., Schwaber, J., Latte, S.A. and Herzenberg, L.A. The Human T Cell Antigen Leu-2(T8) is Encoded on chromosome 2. Human Genetics, in press, 1985.

Chu, A.C., Patterson, J.A.K., Goldstein, G., Berger, C.L., Takezaki, S. and Edelson, R.L. Thymopoietin-like Substance in Human Skin. J. Invest. Dermatol., 81:194-197, 1983.

Cianciolo, G.J., Bogerd, H., Kipnis, R.J., Copelan, T., Oroszlan, S. and Snyderman, R. Inhibition of Lymphocyte Proliferation by a Synthetic Peptide Homologous to Envelope Proteins of Human and Animal Retroviruses. Clin. Res., 33:609, 1985a.

Cianciolo, G.J., Kipnis, R.J., and Snyderman, R. Similarity Between p15E of Murine and Feline Leukemia Viruses and p21 of HTLV. Nature, 311:515, 1984a.

Cianciolo, G.J., Phipps, D. and Snyderman, R. Human Malignant and Mitogen-Transformed Cells Contain Retroviral p15E-Related Antigen. J. Exp. Med., 159: 964-969, 1984b.

Cone, R.E. and Beaman, D. T Cell Antigen Binding Proteins and Their Cell Membrane Analogues In: Antigen-Specific T Cell Receptors and Factors. Ed.: J.M. Marchalonis, CRC Press, in press, 1985.

Croce, G.M., Isobe, M., Palumbo, A., Puck, J., Milng, J., Tweardy, D., Erickson, J., Davis, M.M. and Rovera, G. Gene for Alpha Chain of Human T-Cell Receptor: Location on Chromosome 14 Region Involved in T-Cell Neoplasms. Science, 227: 1044-1047, 1985.

Daynes, R.A., Burnham, D.K., DeWitt, C.W., Roberts, L.K. and Krueger, G.G. The Immunobiology of UVR Carcinogenesis. Cancer Surveys, in press, 1985a.

Daynes, R.A., Emam, M., Krueger, G.G. and Roberts, L.K. Expression of Ia Antigen on Epidermal Keratinocytes After the Grafting of Normal Skin to Nude Mice. J. Immunol., 130:1536-1539, 1983.

Daynes, R.A., Spangrude, G.J., Roberts, L.K. and Krueger, G.G. Regulation by the Skin of Lymphoid Cell Recirculation and Localization Properties. J. Invest. Dermatol., in press, 1985b.

Detels, R., Visscher, B.R., Fahey, J.L., Schwartz, K., Greene, R.S., Madden, D.L., Sever, J.L. and Gottlieb, M.S. The Relation of Cytomegalovirus and Epstein-Barr Virus Antibodies to T-Cell Subsets in Homosexually Active Men. J. Am. Med. Assoc., 251:1719-1722, 1984.

Doyle, A., Martin, W.J., Funa, K., Gazdar, A., Carney, D., Martin, S.E., Linnoila, I., Cuttitta, F., Mulshine J., Bunn, P. and Minna J. Markedly Decreased Expression of Class I Histocompatibility Antigens, Protein and mRNA in Human Small-Cell Lung Cancer. J. Exp. Med., 161:1135-1151, 1985.

Drebin, J.A., Link, V.C., Stern, D.F., Weinberg, R.A. and Greene, M.I. Down-Modulation of an Oncogene Protein Product and Reversion of the Transformed Phenotype by Monoclonal Antibodies. Cell, in press, 1985.

Edelson, R.L. and Fink, J.M. The Immunologic Function of Skin. Sci. Amer., 252:46-53, June 1985.

El-Sadr, W., Stahl, R., Sidhu, G. and Zolla-Pazner, S. The Acquired Immune Deficiency Syndrome: A Review. Laboratory Findings, Clinical Features and Leading Hypotheses. Diagnostic Immunol., 2:73-85, 1984.

Engelman, R.W., Fulton, R.W., Good, R.A., and Day, N.K. Suppression of Gamma Interferon Production by Inactivated Feline Leukemia Virus. Science, 227: 1368-1370, 1985.

Fabbi, M., Acuto, O., Smart, J.E. and Reinherz, E.L. Homology of Ti Alpha-Subunit of a T-Cell Antigen-MHC Receptor with Immunoglobulin. Nature, 312:269-271, 1984.

Fahey, J.L., Prince, J.E., Weaver, M., Groopman, J., Visscher, B.R., Schwartz, R. and Detels, R. Quantitative Changes in Th or Ts Lymphocyte Subsets that Distinguish AIDS Syndromes from Other Immune Subset Disorders. Am. J. Med., 76:95-100, 1984.

Fitch, F.W., Lauchi, D.W., Dialynos, D.P and Wilde, D.B. Contribution of Cloned T Cells Toward an Understanding of the Mechanisms of T-Cell Stimulation by Antigen. Prog. Immunol., 5:745-768, 1983.

Flotte, T., Springer, T.A. and Thorbecke, G.J. Dendritic Cell and Macrophage Staining by Monoclonal Antibodies in Tissue Sections and Epidermal Sheets. Am. J. Pathol., 111:112-124, 1983.

Flug, F., Pelicci, D.G., Bonetti, F., Knowles, D.M. and Dalla-Favera, R. T Cell Receptor Gene Rearrangements as Markers of Lineage and Clonality in T Cell Neoplasms. Proc. Natl. Acad. Sci., USA, 82:3460-3464. 1985.

Gahring, L., Baltz, M., Pepys, M.B. and Daynes, R. Effect of Ultraviolet Radiation on Production of Epidermal Cell Thymocyte-Activating Factor/Interleukin 1 In Vivo and In Vitro. Proc. Natl. Acad. Sci., USA, 81:1198-1202, 1984.

Gahring, L.C., Sholly, S.P., Sauder, D.N. and Daynes, R.A. A Proposed Central Role for Interleukin 1 in the Immunologic Modifications of Experimental Animals Following Exposure to Ultraviolet Radiation, In: Experimental and Clinical Photoimmunology, CRC Press, in press, 1985.

Gelmann, E.P., Preble, O.T., Steis, R., Lane, H.C., Rook, A.H., Wesley, M., Jacob, J., Fauci, A.S., Masur, H. and Longo, D. Human Lymphoblastoid Interferon Treatment of Kaposi's Sarcoma in AIDS: Clinical Response and Prognostic Parameters. Am. J. Med., in press, 1985.

Goverman, J., Minard, K., Shastri, N., Hunkapiller, T., Hausburg, D., Sercarz, E. and Hood, L. Rearranged Beta T Cell Receptor Genes in a Helper T Cell Clone Specific for Lysozyme: No Correlation between V3 and MHC Restriction. Cell, 40:859-867, 1985.

Gottlieb, P.D. Genetic Correlation of a Mouse Light Chain Variable Region Marker with a Thymocyte Surface Antigen. J. Exp. Med., 140:1432-1437, 1974.

Granstein, R.D. and Green, M.I. Splenic I-J-Bearing Antigen-Presenting Cells in Activation of Suppression: Further Characterization. Cell. Immunol., 90, in press, 1985.

Granstein, R.D., Lowy, A. and Greene, M.I. Epidermal Antigen-Presenting Cells in Activation of Suppressor Lymphocytes: Identification of a New Functional Type of Ultraviolet Radiation-Resistant Epidermal Cell. J. Immunol., 132: 563-565, 1984a.

Granstein, R.D., Parrish, H.A., McAuliffe, D.J. and Greene, M.I. Immunologic Inhibition of Ultraviolet Radiation-Induced Suppressor Cell Activation. Science, 224:615-617, 1984b.

Groopman, J., Gottlieb, M.S., Goodman, J., Mitsuyasu, R., Conant, M., Prince, H.E., Fahey, J.L., Derezin, M., Rothman, J., Weinstein, W., Rudnick, S., and Volberding, P. Recombinant Alpha Interferon Therapy of Kaposi Sarcoma Associated with Acquired Immunodeficiency Syndrome. Ann. Int. Med., 100: 671-676, 1984.

Gurish, M.F., Lynch, D.H., Yowell, R. and Daynes, R.A. Abrogation of Epidermal Antigen-Presenting Cell Function by Ultraviolet Radiation Administered In Vivo. Transplantation, 36:304-309, 1983.

Haines, K.A., Flotte, T.A., Springer, T.A., Gigli, I. and Thorbecke, G.J. Staining of Langerhans Cells with Monoclonal Antibodies to Macrophages and Lymphoid Cells. Proc. Natl. Acad. Sci., USA, 80:3448-3451, 1983.

Hannum, C.H., Kappler, J.W., Trowbridge, I.S., Marrack, P. and Freed, J.F. Immunoglobulin-like Nature of the Alpha-Chain of a Human T-Cell Antigen/MHC Receptor. Nature, 312:65-67, 1984.

Harrell, R.A., Cianciolo, G.J., Copelan, T., Oroszlan, S. and Snyderman, R. Suppression of Human Monocyte Superoxide Anion Release by a Synthetic Peptide Homologous to Envelope Proteins of Human and Animal Retroviruses. Clin. Res. 33:452, 1985.

Hayday, A.C., Saito, H., Gillies, D.M., Kranz, D.M., Tanigawa, G., Eisen, H.N. and Tonegawa, S. Structure, Organization and Somatic Rearrangement of T cell Gamma Genes. Cell, 40-259-269, 1985.

Haynes, B.F. Phenotypic Characterization and Ontogeny of Components of the Human Thymic Microenvironment. Clin. Res., in press, 1985a.

Haynes, B.F. The Human Thymic Microenvironment. Adv. Immunol., in press, 1985b.

Haynes, B.F., Palker, T.J., Robert-Guroff, M., Kalyanaraman, V.S., Gallo, R.C., Bolognesi, D.P. and Scearce, R.M. Monoclonal Antibodies Against Human T Cell Leukemia/Lymphoma Virus p19 and p24 Internal Core Proteins. Spectrum of Normal Tissue Reactivity and Use as Diagnostic Probes. In: Human T Cell Leukemia/Lymphoma Viruses, Eds. R. Gallo and M. Essex, Cold Spring Harbor Laboratory, pp 197-203, 1984a.

Haynes, B.F., Scearce, R.M., Lobach, D.F. and Hensley, L.L. Phenotypic Characterization and Ontogeny of Mesodermal-Derived and Endocrine Epithelial Components of the Human Thymic Microenvironment. J. Exp. Med., 159:1149-1168, 1984b.

Hedrick, S.M., Germain, R.N. and Bevan, M.J., Dorf, M., Engel, I., Fink, P., Gascoigne, N., Herber-Katz, E., Kapp, J., Kaufman, Y., Kaye, J., Melchers, F., Pierce, C., Schwartz, R.H., Sorensen, C., Taniguchi, M. and Davis, M.M. Rearrangement and Transcription of a T Cell Receptor Beta Chain Gene in Different T Cell Subsets. Proc. Natl. Acad. Sci., USA, 82:531-535, 1985.

Hedrick, S.M., Nielsen, E.A., Kavaler, J., Cohen, D.I. and Davis, M.M. Sequence Relationships Between Putative T-Cell Receptor Polypeptides and Immunoglobulins. Nature, 308:153-158, 1984.

Hersh, E.M. Gutterman, J.U., Spector, S., Friedman, H., Greenberg, S., Reuben, J.M., LaPushin, R., Matza, M. and Mansell, P.W.A. Impaired In Vitro Interferon, Blastogenic and Natural Killer Cell Responses to Viral Stimulation in Acquired Immune Deficiency Syndrome. Cancer Res., 45:406-410, 1985a.

Hersh, E.M., Mansell, P.W.A., Reuben, J.M., Rios, A. and Newell, G.R. Immunological Characterizations of Patients with AIDS, the AIDS-Related Symptom Complex and an AIDS-Related Life Style. Cancer Res., 44:5894-5902, 1984.

Hersh, E.M., Reuben, J.M., Mansell, P.W.A., Rios, A., Gutterman, J.U., Munn, C.G., Murray, J.L., Spector, S.P., Goldstein, A.L. and Newell, G.R. Immunological Studies of the Acquired Immune Deficiency Syndrome. Relationship of Immunodeficiency to Extent of Disease. Ann. N. Y. Acad. Sci., 437:364-372, 1985b.

Hudig, D., Haverty, T., Fulcher, C., Redelman, D., and Mendelsohn, J. Inhibition of Human Natural Cytotoxicity by Macromolecular Antiproteinases. J. Immunol., 12:1560-1564, 1981.

Hudig, D., Redelman, D., and Minning, L. The Requirement for Proteinase Activity for Human Lymphocyte-Mediated Natural Cytotoxicity (NK): Evidence that the Protineinase Is Serine Dependent and Has Aromatic Amino Acid Specificity of Cleavage. J. Immunol., 133:2647-2654, 1984.

Inaba, K., Steinman, R.M., Van Voorhis, W.C. and Muramatsu, S. Dendritic Cells Are Critical Accessory Cells for Thymus-Dependent Antibody Responses in Mouse and in Man. Proc. Natl. Acad. Sci., USA, 80:6041-6045, 1983.

Isobe, G., Erickson, J., Emanuel, B.S., Nowell, P.C. and Croce, C.M. Location of Gene for Beta Subunit of Human T-Cell Receptor at Band 7q35, a Region Prone to Rearrangement in T cells. Science, 228:580-582, 1985.

Jones, C., Morse, H.G., Kao, F.-T. Carbone, A. and Palmer, E. Human T-Cell Receptor Alpha Chain Genes: Location on Chromosome 14. Science, 228:83-85, 1985.

Kappler, J., Kubo, R., Haskins, K., Hannum, C., Marrack, P., Pigeon, M., McIntyre B., Allison, J. and Trowbridge, I. The MHC-Restricted Antigen Receptor on T-Cells in Mouse and Man. Cell, 35:295-312, 1983.

Kaye, J. and Janeway, C.A. The Fab Fragment of a Directly Activating Monoclonal Antibody that Precipitates a Disulfide-Linked Heterodimer From a Helper T Cell Clone Blocks Activation by Either Allogeneic Ia or Antigen and Self-Ia. J. Exp. Med., 159:1397-1412, 1984.

Kranz, D.M., Saito, H., Disteche, C.M., Swisshelm, K., Pravtcheva, D., Ruddle, F.H., Eisen, H.N. and Tonegawa, S. Chromosomal Locations of the Murine T Cell Receptor Alpha-Chain and Gamma-Chain Genes. Science, in press, 1985.

Kranz, D.M., Sherman, D.H., Litkovsky, M.W., Pasternack, M.S. and Eisen, H.N. Immunoprecipitation of All Surface Structures of Cloned Cytotoxic T Lymphocytes by Clone-Specific Antisera. Proc. Natl. Acad. Sci., USA, 81:573-577, 1984a.

Kranz, D.M., Tonegawa, S. and Eisen, H.N. Attachment of an Anti-Receptor Antibody to Non-Target Cells Renders Them Susceptible to Lysis by a Clone of Cytotoxic T Lymphocytes. Proc. Natl. Acad. Sci., USA, 81:1154-1157, 1984b.

Kreiss, J.K., Kasper, C.K., Fahey, J.L., Weaver, M., Lawrence, D.N., Stewart, J.A. and Visscher, B.R. Nontransmission of T-Cell Subset Abnormalities from Hemophiliacs to Their Spouses. J. Am. Med. Assoc., 251:1450-1454, 1984.

Krueger, G.G., Daynes, R.A. and Emam, M. Biology of Langerhans Cells: Selective Migration of Langerhans Cells into Allogeneic and Xenogeneic Grafts on Nude Mice. Proc. Natl. Acad. Sci., USA, 80: 1650-1654, 1983.

Lancki, D.W., Loiber, M., Loken, M.R. and Fitch, F.W. A Clone-Specific Monoclonal Antibody that Inhibits Cytolysis of a Cytolytic T Cell Clone. J. Exp. Med., 157:921-936, 1983.

Lee, N.E., D'Eustachio, P., Pravtcheva, D., Ruddle, F.H., Hedrick, S.M. and Davis, M.M. Murine T Cell Receptor Beta Chain is Encoded on Chromosome 6. J. Exp. Med., 160:905-913, 1984.

Leonard, J.E., Taetle, R. and Ryner, K. Preclinical Studies on the Use of Selective Antibody-Ricin Conjugates in Autologous Bone Marrow Transplantation. Blood, in press, 1985.

Lobach, D.F., Scearce, R.M. and Haynes, B.F. The Human Thymic Microenvironment. Phenotyopic Characterization of Hassall's Bodies Using Monoclonal Antibodies. J. Immunol., 134:250-257, 1985.

Malissen, M., Minard, K., Niolsness, S., Kronenberg, M., Governmen, J., Hunkapiller, T., Prystowsky, M.B., Yoshikai, Y., Fitch, F., Mak, T.W. and Hood, L. Mouse T Cell Antigen Receptor: Structure and Organization of Constant and Joining Gene Segments Encoding the Beta Polypeptide. Cell, 37: 1107-1110, 1984.

Marchalonis, J.J. Antigen-Binding Molecules of T Cells: Distinction from MHC-Restricted Molecules and Segmental Homology to Immunoglobulin V_H and T-Cell Receptor Genes. Scand. J. Immunol., 21:99-107, 1985.

McFarland, E.J., Scearce, R.M. and Haynes, B.F. The Human Thymic Microenvironment. Cortical Thymic Epithelium is an Antigenically Distinct Region of the Thymic Microenvironment. J. Immunol., 133:1241-1249, 1984.

McIntire, B.W. and Allison, J.P. Biosynthesis and Processing of Murine T-Cell Antigen Receptor. Cell, 38:159-166, 1984.

Mertelsmann, R. and Welte, K. Human Interleukin 2. Clin. Immunol. Allergy, 4:393-413, 1984.

Mertelsmann, R., Welte, K., Sternberg, C., O'Reilly, R., Moore, M.A.S., Clarkson, B.D. and Oettgen, H.F. Treatment of Immunodeficiency with Interleukin 2: Initial Exploration. J. Biol. Res. Mod., 4:483-490, 1984.

Meuer, S.C., Acuto, O., Hussey, R.E., Hodgdon, J.D., Fitzgerald, K.A., Schlossman, S.F. and Reinherz, E.L. Evidence for the T3-Associated 90K Heterodimer as the T-Cell Antigen Receptor. Nature, 303:808-811, 1983a.

Meuer, S.C., Fitzgerald, K.A., Hussey, R.E., Hodgdon, J.C., Schlossman, S.F. and Reinherz, E.L. Clonotypic Structures Involved in Antigen Specific Human T Cell Function: Relationship to the T3 Molecular Complex. J. Exp. Med., 157:705-719, 1983b.

Meuer, S.C., Hussey, R.E., Hodgdon, J.C., Hercend, T., Schlossman, S.F. and Reinherz, E.L. Surface Structures Involved in Target Recognition by Human Cytotoxic Lymphocytes. Science, 218:471-474, 1982a.

Meuer, S.C., Schlossman, S.F. and Reinherz, E.L. Clonal Analysis of Human Cytotoxic T Lymphocytes: T4 and T8 Effector T Cells Recognize Products of Different Major Histocompatibility Regions. Proc. Natl Acad. Sci., USA, 79:4395-4400, 1982b.

Minden, M.D., Toyonaga, B., Ha, K., Yanagi, Y., Chin, B., Gelfand, E. and Mak, T. Somatic Rearrangement of T-Cell Antigen Receptor Gene in Human T-Cell Malignancies. Proc. Natl. Acad. Sci., USA, 82:1224-1227, 1985.

Munn, C.G., Reuben, J.M., Hersh, E.M., Mansell, P.W.A and Newell, G.R. T Cell Surface Antigen Expression on Lymphocytes of Patients with AIDS During In Vitro Mitogen Stimulation. J. Immunol., in press, 1985.

Nair, M.P.N., Schwartz, S.A. and Laing, T.J. Decreased Natural and Antibody-Dependent Cellular Cytotoxic Activities in Intravenous Drug Abusers. Clin. Immunol. Immunopathol., in press, 1985.

Nelson, M., Nelson, D.S., Spradbrow, P.B., Kuchroo, V.K., Jennings, P.A., Cianciolo, G.J., and Snyderman, R. Successful Tumour Immunotherapy: Possible Role of Antibodies to Anti-Inflammatory Factors Produced by Neoplasms. Clin. Exp. Immunol., in press, 1985.

Newell, G.R., Mansell, P.W.A., Wilson, M.B., Lynch, H.K., Spitz, M.R. and Hersh, E.M. Risk Factor Analysis Among Men Referred for Possible Acquired Immune Deficiency Syndrome. Preventive Med., in press, 1985.

Oettgen, H.C., Terhorst, C., Cauthey, L.C. and Rosoff, P.M. Stimulation of the T3-T Cell Receptor Complex Induces a Membrane-Potential Sensitive Calcium Influx. Cell, 40:583-590, 1985.

Orosz, C.G., Zinn, N.E., Olsen, R.G. and Mathes, L.E. Retrovirus-Mediated Immunosuppression. I FeLV-UV and Specific FeLV Proteins Alter T Lymphocyte Behavior by Inducing Hyporesponsiveness to Lymphokines. J. Immunol., 134:3396-3402, 1985.

Palker, T.J., Scearce, R.M., Miller, S.E., Popovic, M., Bolognesi, D.P., Gallo, R.C. and Haynes, B.F. Monoclonal Antibodies against Human T Cell Leukemia/Lymphoma Virus (HTLV) p24 Internal Core Protein: Use as Diagnostic Probes and Cellular Localization of HTLV. J. Exp. Med., 159:1117-1131, 1984.

Pasternack, M.D. and Eisen, H.N. A Novel Serine Esterase Expressed by Cytotoxic T Lymphocytes. Nature, 314:743-745, 1985.

Patterson, J.A.K., Eisinger, M., Haynes, B.F., Berger, C.L. and Edelson, R.L. Monoclonal Antibody 4F2 Reactive with Basal Layer Keratinocytes: Studies in the Normal and Hyperproliferative State. J. Invest. Dermatol. 83:210-213, 1984.

Pernis, B. and Axel, R. A One-and-a-Half Receptor Model for MHC-Restricted Antigen Recognition by T Lymphocytes. Cell, 41:13-16, 1985.

Posnett, D.N., Prigler, R.D., Bushkin, Y., Fisher, D.E., Mayer, L.F., Chiorazzi, N. and Kunkel, H.G. T Cell Anti-Idiotypic Antibodies Reveal Differences Between Two Human Leukemias. J. Exp. Med., 160:494-505, 1984.

Preble, O.T., Rook, A.H., Quinnan, G.V., Vilcek, J., Friedman, R.M., Steis, R., Gelmann, E.P. and Sonnabend, J.A. The Role of Interferon in AIDS. Ann. N.Y. Acad. Sci., 437:65-75, 1984.

Preble, O.T., Rook, A.H., Steis, R., Silverman, R.H., Krause, D., Quinnan, G.V., Masur, H., Jacob, J., Longo, D., and Gelmann, E.P. Interferon-Induced 2'-5' Oligoadenylate Synthetase During Alpha Interferon Therapy in Homosexual Men with Kaposi's Sarcoma: Marked Deficiency in Biochemical Response to Interferon in AIDS Patients. J. Infect. Dis., in press, 1985.

Prince, H.E., Kermani-Arab, V. and Fahey, J.L. Depressed Interleukin-2 Receptor Expression in Acquired Immune Deficiency and Lymphadenopathy Syndromes. J. Immunol., 133:1313-1317, 1984.

Prince, J., Moody, O., Shubin, B. and Fahey, J.L. Defective Monocyte Function in AIDS: Evidence from Monocyte-Dependent T Cell Proliferative System. J. Clin. Immunol., 5:21-25, 1985.

Ragni, M.V., Winkelstein, A., Evans, T.L., Lewis, J.H., Bontempo, F.A., Spero, J.A. and Rabi, B.S. T Lymphocyte Colony Assay in Hemophiliacs. Blood, 64:105-109, 1984.

Raulet, D.H., Gorman, R.D., Saito, H. and Tonegawa, S. Developmental Regulation of T-Cell Receptor Gene Expression. Nature, 314:103-107, 1985.

Redelman, D. and Hudig, D. Killing by Murine Cytotoxic Lymphocytes: The Involvement of Thiols and Activated Protease. J. Immunol. 124:870-878, 1980.

Redelman, D. and Hudig, D. The Mechanism of Cell-Mediated Cytotoxicity III. Protease-Specific Inhibitors Preferentially Block Later Events in CTL-Mediated Lysis Than Do Inhibitors of Methylation or Thiol-Specific Reagents. Cell. Immunol., 81:9-21, 1983.

Reinherz, E.L., Cooper, M.D., Schlossman, S.F. and Rosen, F.S. Abnormalities of T Cell Maturation and Regulation in Human Beings with Immunodeficiency Disorders. J. Clin. Invest., 68:699-705, 1981.

Reinherz, E.L., Kung, P.C., Goldstein, G., Levey, R.H and Schlossman, S.F. Discrete Stages of Human Intrathymic Differentiation: Analysis of Normal Thymocytes and Leukemic Lymphoblasts of T Lineage. Proc. Natl. Acad. Sci., USA, 77:1588-1592, 1980.

Reinherz, E.L., Meuer, S.C., Fitzgerald, K.A., Hussey, R.E., Levine, H. and Schlossman, S.F. Antigen Recognition by Human T Lymphocytes is Linked to Surface Expression of the T3 Molecular Complex. Cell, 30:735-743, 1982.

Reinherz, E.L., Meuer, S.C. and Schlossman, S.F. Delineation of Antigen Receptors on Human Lymphocytes. Immunol. Today, 4:5-8, 1983.

Reuben, J.M., Hersh, E.M., Murray, J.L., Munn, C.G., Mehta, R., Mansell, P.W.A. and Newell, G.R. IL-2 Production and Response In Vitro by the Leukocytes of Patients with Acquired Immune Deficiency Syndrome. J. Immunol., in press, 1985.

Ritz, J., Bast, R.C., Clavell, L.A., Hercend, T., Sallan, S.E., Lipton, J.M., Feeney, M., Nathan, D.G. and Schlossman, S.F. Autologous Bone Marrow Transplantation in CALLA-Positive Acute Lymphoblastic Leukemia After In Vitro Treatment with J5 Monoclonal Antibody and Complement. Lancet, 2:60-63, 1982.

Ritz, J., Campen, T.J., Schmidt, R.E., Royer, H.D., Hercend, T., Hussey, R.E. and Reinherz, E.L. Analysis of T-Cell Receptor Gene Rearrangement and Expression in Human Natural Killer Clones. Science, 228:1540-1543, 1985.

Roberts, L.K., Daynes, R.A. and Krueger, G.G. The Potential Immunologic Role of Keratinocytes that Express Ia Antigens. Clin. Res., 32:143A, 1984.

Roberts, L.K., Krueger, G.G. and Daynes, R.A. Correlation Between the Inducible Keratinocyte Expression of Ia and the Movement of Langerhans Cells into the Epidermis. J. Immunol., 134:3781-3784, 1985.

Royer, H.D., Acuto, O., Fabbi, M., Tizard, R., Ramachandran, K., Smart, J.E. and Reinherz, E.L. Genes Encoding the Ti Beta Subunit of the Antigen/MHC Receptor Undergo Rearrangement During Intrathymic Ontogeny Prior to Surface T3-Ti Expression. Cell, 39:261-266, 1984.

Saito, H., Kranz, D.M., Takagaki, Y., Hayday, A.C., Eisen, H.N. and Tonegawa, S. Complete Primary Structure of a Heterodimeric T Cell Receptor Derived from cDNA Sequences. Nature, 309:757-762, 1984a.

Saito, H., Kranz, D.M., Takagaki, Y., Hayday, A.C., Eisen, H.N. and Tonegawa, S. A Third Rearranged and Expressed Gene in a Clone of Cytotoxic T Lymphocytes. Nature, 312:36-39, 1984b.

Salazar-Gonzales, J.F., Moody, D.J. and Fahey, J.L. Lymphocyte Ecto-5'-Nucleotidase Deficiency in the Acquired Immune Deficiency Syndrome: Evidence of Immaturity and Activation in CD8 (T-Suppressor/Cytotoxic) Lymphocytes. J. Immunol., in press, 1985.

Schwarz, H., Thiel, H.-J., Weinhold, K.J. and Bolognesi, D.P. Stimulation of Immunoreactivity Against Leukemia of Older AKR Mice by Treatment with Antibodies Against Retroviral Surface Components. Role of p15(E) Antibody. Z. Naturforch., 39:1199-1202, 1984.

Seligmann, M., Chess, L., Fahey, J.L., Fauci, A.S., Lachmann, P., L'Age-Stehr, J., Ngu, J., Pinching, A.J., Rosen, F.S., Spira, R.J. and Wybran, J. AIDS: An Immunologic Reevaluation. N. Eng. J. Med., 311:1286-1292, 1984.

Shastri, N., Miller, A. and Sercarz, E.E. The Expressed T Cell Repertoire is Hierarchical: The Precise Focus of Lysozyme-Specific T Cell Clones is Dependent Upon the Structure of the Immunogen. J. Mol. Cell. Immunol., 1:369-379, 1984.

Snodgrass, H.R., Dembic, Z., Steinmetz, M. and Bechmer, H. Expression of T-Cell Antigen Receptor Genes During Fetal Development in the Thymus. Nature, 315:232-233, 1985.

Snyderman, R. and Cianciolo, G.J. Immunosuppressive Activity of the Retroviral Envelope Protein p15E and Its Possible Relationship to Neoplasia. Immunol. Today., 5:240-244, 1984

Spangrude, G.J., Araneo, B.A. and Daynes, R.A. Site-Selective Homing of Antigen-Primed Lymphocyte Populations Can Play a Crucial Role in the Efferent Limb of Cell-Mediated Immune Responses In Vivo. J. Immunol., 134:2900-2907, 1985.

Spangrude, G.J., Bernhard, E.J., Ajioka, R.S. and Daynes, R.A. Alterations in Lymphocyte Homing Patterns Within Mice Exposed to Ultraviolet Radiation. J. Immunol., 130:2974-2981, 1983.

Staerz, V.D., Kanagawa, O. and Bevan, M.J. Hybrid Antibodies Can Target Sites for Attack by T Cells. Nature, 314:628-631, 1985a.

Sykora, K.W., Kolitz, J., Szabo, P., Grzeschik, H-H., Moore, M.A.S. and Mertelsmann, R. The Human IL2 Gene Is Located On Chromosome 4. Cancer Invest., 2:261-265, 1984.

Staerz, V.D., Rammensee, H-G., Benedetto, J.D. and Bevan, M.J. Characterization of a Murine Monoclonal Antibody Specific for an Allotypic Determinant on T Cell Antigen Receptor. J. Immunol., 134:3994-4000, 1985b.

Sukhatue, V.P., Sizer, V.C., Vollmer, A.C., Hunkapiller, T. and Paines, J.R. The T Cell Differentiation Antigen Leu 2/T8 Is Homologous to Immunoglobulin and T Cell Receptor Variable Regions. Cell, 40:591-597, 1985.

Sukhatue, V.P., Vollmer, A.C., Erickson, J., Isobe, M., Croce, C. and Paines, J.R. Gene for the Human T-Cell Differentiation Antigen Leu-2/T8 Is Closely Linked to the Light Chain Locus on Chromosome 2. J. Exp. Med., 161:429-434, 1985.

Valentine, F.T and Paolina, A. Cell Lines of B-Cell Lineage Established from the Blood of Patients with AIDS and ARC. International Meeting on AIDS, Atlanta, in press, 1985.

Van Voorhis, W.C., Witmer, M.D. and Steinman, R.M. The Phenotype of Dendritic Cells and Macrophages. Fed. Proc., 42:3114-3118, 1983.

Wallich, R., Bulbuc, N., Hammerling, G.J., Katzar, S., Segal, S. and Feldman, M. Abrogation of Metastatic Properties of Tumour Cells by De Novo Expression of H-2K Antigens Following H-2 Gene Transfection. Nature, 315:301-305, 1985.

Welte, K. and Mertelsmann, R. Human Interleukin 2: Biochemistry, Physiology and Possible Pathogenetic Role in Immunodeficiency Syndromes. Cancer Invest. 3:35-49, 1985.

Winkelstein, A., Klein, R.S., Evans, T.L., Dixon, B.W., Holder, W.L. and Weaver, L.D. Defective In Vitro T Cell Colony Formation in the Acquired Immunodeficiency Syndrome. J. Immunol., 134:151-156, 1985.

Yanagi Y., Yoshikai Y., Legget K., Clark, S.P., Aleksander, I. and Mak, T.W. A Human T Cell Specific cDNA clone Encodes a Protein Having Extensive Homology to Immunoglobulin Chains. Nature, 308:145-149, 1984.

Yunis, J.J. The Chromosomal Basis of Human Neoplasia. Science, 221:227-233, 1983.

Zolla-Pazner, S. B Cells in the Pathogenesis of AIDS, Immunol. Today, 5:289-291, 1984.

MYELOMA PROTEINS (AB)

R01 CA08497 Abnormal Proteins in Multiple Myeloma
Putnam Indiana University, Bloomington

R01 CA10056 Proteins in Multiple Myeloma and Related Blood Diseases
Solomon University of Tennessee, Knoxville

R01 CA12421 Immunoglobulin Genes and Oncogenes in Lymphoid Tumors
Adams Walter and Eliza Hall Inst. of Medical Research

R01 CA13014 Studies on Proteins of Plasma Cell Cancers
Beychok Columbia University

R01 CA16858 Genetics and Biochemistry of Myeloma Ig Production
Morrison Columbia University

R01 CA19616 Immunoglobulins in Multiple Myeloma and Amyloidosis
Edmundson University of Utah

R01 CA24432 Sequence, Shape and Specificity of Antibodies
Haber Massachusetts General Hospital

R01 CA25754 Control of Immunoglobulin Synthesis
Storb University of Washington

R01 CA32582 Studies on Secretory Immunoglobulin
Lamm Case Western Reserve University

R01 CA34012 Differentiation Defects in Malignancies of the B Cell
Vogler Vanderbilt University

R01 CA34778 Analysis of Nonsmall Cell Lung Carcinoma Antigens
Walker Scripps Clinic and Research Foundation

R01 CA36606 Immunoglobulin Gene Expression in Myeloma Mutants
Milcarek University of Pittsburgh

CELL SURFACE ANTIGENS (AG)

R01 CA12851 Embryonic and Virally Induced Tumor-Cell Membrane Antigens
Sanders University of Texas, Austin

R01 CA13287 Genetic Basis of Antigenic Variation
Hyman Salk Institute for Biological Studies

R01 CA18600 Masking of Antigens at Cancer Cell Surfaces
Codington Massachusetts General Hospital

R01 CA18734 Immunologic Studies Related to Malignancy
Jones University of Colorado Health Sciences Center

R01 CA19224 Relation of Blood Group and Human Tumor Antigen
Hakomori Fred Hutchinson Cancer Research Center

P01 CA19265 UCCRC: Chromosome Metabolism in Cancer Biology
Ultmann University of Chicago

P01 CA19266 UCCRC: Lymphoma and Leukemia Clinical Research Program
Ultmann University of Chicago

R01 CA20500 Structural and Serological Studies on IA Antigens
Cullen Washington University

R01 CA21445 Antigens of Malignant Melanoma and Other Human Tumors
Lloyd Sloan-Kettering Institute for Cancer Research

R01 CA22540 Nature of T-Specific Human Carcinoma Antigens
Springer Evanston Hospital

R01 CA23568 Immunoresponse to Human Surface Antigens
Croce Wistar Institute of Anatomy and Biology

R01 CA23770 Antigen-Induced Lymphoma
Haughton University of North Carolina, Chapel Hill

R01 CA24358 Leukemia Associated Antigens
Billing University of California, Los Angeles

P01 CA25874 Human Melanoma and Tumor Specific Monoclonal Antibodies
Koprowski Wistar Institute of Anatomy and Biology

R01 CA27416 Characterization of New Human IA and Leukemia Antigen
Mohanakumar Virginia Commonwealth University

R01 CA28420 Molecular Profile of Human Melanoma Antigens
Reisfeld Scripps Clinic and Research Foundation

R01 CA28461 Cell Surface Antigens of Sarcomas
De Leo Sloan-Kettering Institute for Cancer Research

R01 CA28564 Human Squamous Cell Carcinoma: Culture and Serology
Carey University of Michigan at Ann Arbor

R01 CA29964 UNC-CH Immunocytomas
Haughton University of North Carolina, Chapel Hill

R01 CA30266 Membrane Antigen Organization in Tumor Immunity
Gooding Emory University

R01 CA30647 Human Monoclonal Antibodies to OFA-I
Irie University of California, Davis

R01 CA31620 Inappropriate H-2 (K/D) and IE/C Antigens on Tumors
Bonavida University of California, Los Angeles

R01 CA31828 Immune Response to Syngeneic Leukemic B-Cell Antigens
Ricardo Wake Forest University

R01 CA32132 Autoimmunity to Testicular Germ Cell Oncofetal Antigens
Anderson Dana-Farber Cancer Institute

R01 CA32632 Glycoconjugate Structure and Function in Leukocytes
Klock Medical Research Institute of San Francisco

R01 CA33529 Processing of IA Molecules in B-Cells and Macrophages
Cullen Washington University

R01 CA33693 MHC Coded Alloantigens on Lung Tumors
Martin U.S. Uniformed Services Univ. of Health Sciences

R01 CA34031 Analysis of Human Prostate Carcinoma Associated Antigens
Ng Columbia University

R01 CA34232 Expression of H-2 Antigens on SJL/J Tumors
Beisel Johns Hopkins University

R01 CA34342 Selecting Expressed Tumor Immune RNA with Hybridomas
Paque University of Texas

R01 CA34368 MHC Antigen Expression on Teratocarcinoma Cells
Ostrand-Rosenberg University of Maryland, Baltimore County

R01 CA34378 Tumor Cytolysis by Mononuclear Leukocytes
Zucker-Franklin New York University

R01 CA34913 Genetics of Response to Histocompatibility Antigens
Howard Institute of Animal Physiology

R01 CA35592 Structure and Function of Cell Surface Hyaluronate
Underhill Georgetown University

R01 CA35929 Monoclonal Antibodies to Human Squamous Cancer Antigens
Carey University of Michigan at Ann Arbor

R01 CA37099 Immunogenetics of Unique Tumor-Specific MHC Antigens
Goodenow University of California, Berkeley

R01 CA37156 Immunobiology of Unique Tumor-Specific Antigens
Schreiber University of Chicago

R01 CA37169 Tumor-Specific CTL Recognition of Transfected Cells
Faller Dana-Farber Cancer Institute

R01 CA37303 Structure-Function Studies of SV40 TSTA and H-2
Pan Wistar Institute of Anatomy and Biology

R01 CA37440 Molecular Studies of Human Melanoma Antigen
Brown Oncogen

R01 CA37645 Function and Structure of Leukemic Cell II
Humphreys University of Massachusetts Medical School

R01 CA38500 Membrane Antigens Which Mediate Metastatic Phenotype
Le Grue University of Texas System Cancer Center

R01 CA39054 Cell Surface Antigens of Murine Tumors
Callahan Colorado State University

R01 CA39612 IL-2 Receptor in the Pathogenesis of Human Lymphoma
Crabtree Stanford University

R01 CA40041 Surface Antigens of Murine Tumors
Allison University of California, Berkeley

R01 CA40134 TI A and B V-Gene Usage in Human T-Cell Malignancies
Reinherz Dana-Farber Cancer Institute

R01 CA40216 Characterization of Human B-Cell Activation Antigens
Nadler Dana-Farber Cancer Institute

R23 CA40311 Characterization of Mammary Carcinoma-Associated Antigen
Imam University of Southern California

R01 CA40524 Characterization of Oncofetal Antigens
Coggin University of South Alabama

R01 CA41993 Immunobiology of MIS Responses
Webb Scripps Clinic and Research Foundation

R01 CA42046 T-Cell Leukemia and the Human T-Cell Antigen Receptor
Posnett Cornell University Medical College

CELL SURFACE DETERMINANTS OF LYMPHOCYTES AND MACROPHAGES (CS)

R01 CA04681 Genetic Studies with Mammalian Cells
Herzenberg Stanford University

R01 CA12851 Embryonic and Viral Induced Tumor Cell Membrane Antigens
Sanders University of Texas, Austin

R01 CA18640 Behavior of Weak Transplantation Antigens
Silvers University of Pennsylvania

R01 CA18659 Chemical, Genetic and Cellular Aspects of Immunogenicity
Gill University of Pittsburgh

P01 CA21112 Clinical and Basic Studies of Plasma Cell Dyscrasias
Osserman Columbia University

R01 CA21651 Teratocarcinoma and Embryonal Tumors: Surface Antigens
Artzt Sloan-Kettering Institute for Cancer Research

R01 CA22131 Immunogenetics of Ly Systems
Boyse Sloan-Kettering Institute for Cancer Research

P01 CA22507 Immunogenetics of the Major Histocompatibility Complex
Dupont Sloan-Kettering Institute for Cancer Research

R01 CA24473 Genetics and Functions of (H-2 Linked) I Region
David Mayo Foundation

R01 CA25044 Surface IgM of Malignant Lymphocytes and Plasma Cells
Hickman Jewish Hospital of St. Louis

R01 CA25532 Glycolipids of Murine and Human Lymphocytes
Schwarting Eunice Kennedy Shriver Center Mental Retardation

R01 CA25613 Membrane Components of the Leukocyte Complement System
Ross University of North Carolina, Chapel Hill

R01 CA25893 Cell Surface Molecules: Hematopoietic Differentiation
Hyman Salk Institute for Biological Studies

R01 CA28533 Mechanisms of Tumor Destruction by Immune Effectors
Russell Washington University

R01 CA29194 Somatic Cell Genetics of Cell Surface Antigens
Rajan Yeshiva University

R01 CA29548 Differentiation Antigens on Human Lymphocytes
Hansen Pacific Northwest Research Foundation

R01 CA29679 Genetic Analysis of Membrane Immunoglobulin
Pious University of Washington

R01 CA30147 Genetic Markers, Leukemogenesis and Thymic Function
Gottlieb University of Texas, Austin

R01 CA30654 Regulation of Immune Responses by FC Portion of Antibody
Morgan Scripps Clinic and Research Foundation

R01 CA31798 Lymphocyte Function-Associated Antigens
Springer Dana-Farber Cancer Institute

R01 CA31799 Chemistry of Tumoricidal Macrophage Surface Antigens
Springer Dana-Farber Cancer Institute

R01 CA34077 IL-2 Action on Normal and Malignant Lymphocyte Receptors
Mendelsohn University of California, San Diego

R01 CA34787 Human Cell Surface Antigens: Transferrin Receptors
Trowbridge Salk Institute for Biological Studies

R01 CA34900 Chemical Analysis of Human and Murine T-Cell Antigens
Wang Medical University of South Carolina

R01 CA35055 QA and TL Antigens Expressions and Function
Flaherty New York State Department of Health

R01 CA35638 Molecular Pathway of Human T-Cell-Mediated Cytotoxicity
Ware University of California

R23 CA35976 Characterization of the Cytotoxic T-Cell Receptor
Hunter University of Alabama in Birmingham

R01 CA35977 FC-Gamma Receptor-Mediated Regulation of Macrophage
Suzuki Univ of Kansas College Health Science and Hospital

R01 CA36137 RADLV Leukemia Antigens Recognized by Cytotoxic T Cells
Oettgen Sloan-Kettering Institute for Cancer Research

R01 CA36167 Surface Antigens of Human Myeloid Progenitor Cells
Griffin Dana-Farber Cancer Institute

R01 CA36700 Structural Studies of the Products of the H-2 Complex
Freed National Jewish Hospital and Research Center

R01 CA37026 Killer Cell Surface Antigens--Biochemistry and Function
Hall Virginia Commonwealth University

R01 CA37155 Receptors for Immunoglobulin G on Leukocytes
Perussia Wistar Institute of Anatomy and Biology

R23 CA37199 Mechanisms of NK Resistance in Tumor Cell Variants
Wright University of California, Los Angeles

R01 CA37827 Analysis of Human NK Function
Kornbluth University of Pennsylvania

R23 CA38055 FC Receptor Expression During Myeloid Differentiation
Fleit State University of New York at Stony Brook

R01 CA38396 The Molecular Basis of T-Cell-Mediated Cytolysis
Redelman University of Nevada, Reno

R01 CA38404 Structural Studies of IA Alloantigens
Silver Hospital for Special Surgery

R01 CA39003 Presentation of Integral Membrane Antigens to TH-Cells
Chesnut National Jewish Hospital and Research Center

R01 CA39064 Cell Surface Antigens on Human Macrophages
Todd University of Michigan at Ann Arbor

R01 CA39069 Cloning H-2I and HLA-D Region Coding Sequences
McDevitt Stanford University

R23 CA39264 Immunobiology of the T-Cell Response to Class I MHC AG
Greenstein Dana-Farber Cancer Institute

R01 CA40040 Surface Antigens of Rat Hepatocellular Carcinomas
Allison University of California, Berkeley

R01 CA40044 Immunological Studies of Membrane Antigens
Metzgar Duke University

R01 CA40294 Antibodies to Hormone Receptors for Cancer Therapy
Sato W. Alton Jones Cell Science Center

HUMORAL FACTORS OTHER THAN ANTIBODY (HF)

R01 CA12779 Leukocyte Regulatory Mechanisms
Nowell University of Pennsylvania

R01 CA15129 A Serum Immunosuppressive Factor in Cancer
Oh Boston University

R01 CA17643 Regulation of T-Cell Proliferation and Differentiation
Smith Dartmouth College

R01 CA17673 Regulation of the Humoral Immune Response by B Cells
Hoffmann Sloan-Kettering Institute

R01 CA22126 Ultraviolet Light Radiation and Immunoregulation
Daynes University of Utah

R01 CA24974 Chemical and Immunological Characteristics of Thymosin
Goldstein George Washington University

R01 CA26143 Control of Complement-Mediated Tumor Cell Cytolysis
Lint Rush University

R01 CA26504 Regulation of Granulocyte and Macrophage Production
Stanley Yeshiva University

R01 CA27903 The Biology of the Antitumor Actions of Interferons
Epstein University of California, San Francisco

R01 CA29991 Interferon Action: Studies on Interferon Receptor System
Gupta Sloan-Kettering Institute for Cancer Research

R01 CA30015 Acute Phase Reactants: Induction and Host Resistance
Mortensen Ohio State University

R01 CA30515 Immunological Aspects of Retinoids in Human Cancer
Sidell University of California, Los Angeles

R01 CA31394 Effect of Interferon Inducers on NK Cell Cytotoxicity
Lotzova University of Texas System Cancer Center

R01 CA33168 Thymic Peptides, Monoclonal Antibodies and Cancer
Incefy Sloan-Kettering Institute for Cancer Research

R23 CA33903 Tumor Produced Macrophage Chemokinetic Factor
Lane Medical College of Ohio at Toledo

R01 CA33956 Physiochemical Studies of Immune Complexes
Colton Massachusetts Institute of Technology

R01 CA33994 Interferon-Induced Immunosuppression and Tumor Rejection
Korngold Wistar Institute of Anatomy and Biology

R01 CA34141 Isolation of Macrophage Agglutination Factor
Godfrey New York Medical College

R01 CA34344 Tumorigenesis: Immunoendocrine Systems Interactions
Michael State University of New York at Albany

R01 CA34573 Studies of Cytolytic Factors from Macrophages
Shands University of Florida

R01 CA34616 Lymphokine Antagonists from Tumor Cell Lines
Stone University of Denver

R01 CA34805 Natural Cytotoxic Activity and Tumorigenesis
Patek Salk Institute for Biological Studies

R01 CA34951 Nerve Growth Factor and Complement Pathway
Boyle University of Florida

R01 CA35152 Cytolytic T-Lymphocyte Helper Factor
Fan University of Minnesota of Minneapolis-St. Paul

R01 CA35761 Mechanism of Melphalan-Mediated Tumor Eradication
Mokyr University of Illinois at Chicago

R23 CA35975 Biochemistry and Biological Role of Lymphotoxins
Klostergaard University of Texas System Cancer Center

R01 CA37003 Role of Complement in IgM-Dependent Leukemia Suppression
Johnson Johns Hopkins University

R01 CA37187 Role of Type I Interferons in Macrophage Activation
Pace University of Florida

R01 CA37385 Structure-Function of Interferon-Gamma and Its Receptors
Yip New York University

R01 CA37670 A B-Cell Growth Factor Produced by a Neoplastic B Cell
Vitetta University of Texas Health Science Center, Dallas

R23 CA37683 Variants of T-Cell Growth Factor From Malignant Cells
Gootenberg Georgetown University

R01 CA37932 Human Lymphokine that Blocks Growth of IA+ Target Cells
Trucco Wistar Institute of Anatomy and Biology

R01 CA37943 Cyclooxygenase Products and Mammary Cancer
Fulton Michigan Cancer Foundation

R01 CA38587 Regulatory and Antitumor Effects of Gamma Interferon
Johnson University of Florida

R01 CA38779 Gamma Interferon Receptor of Tumorolytic Macrophages
Russell University of Florida

R01 CA39048 Production and Purification of Mouse Immune Interferon
Johnson University of Florida

R01 CA39605 Analysis of T-Cell Growth Control by Gene Transfer
Rothenberg California Institute of Technology

R01 CA39888 Lymphokines, Cellular Immunity, Delayed Hypersensitivity
Salvin University of Pittsburgh

R01 CA39925 Mechanism of Gamma Interferon Regulation of IA Antigens
Walker Indiana University-Purdue University at Indianapolis

R01 CA40931 Complement and Immune Complexes in Lymphosarcoma
Day University of South Florida

R01 CA41997 Vasoactive Intestinal Peptide in Diagnosis of Leukemia
O'Dorisio Children's Hospital, Columbus

TUMOR RELATED ANTIBODIES (HI)

R01 CA15064 Immunochemical Studies on Carcinogenic Myocotoxin
Chu University of Wisconsin, Madison

R01 CA26695 Antigen-Specific T-Cell Clones: Generation and Analysis
Cantor Dana-Farber Cancer Institute

R01 CA28149 Immunotherapy of a B-Cell Leukemia (BCLI)
Vitetta University of Texas Health Science Center, Dallas

R01 CA32497 Structure and Genetics of Antibody Variable Regions
Cannon University of Massachusetts Medical School

R01 CA34079 Specificity of Monoclonal Antibodies to Human Cancer
Houghton Sloan-Kettering Institute for Cancer Research

R01 CA35525 Molecular Mechanisms of Induced Immune Cytolysis
Vogel Georgetown University

R23 CA35692 The Mechanism of Immunotoxin Internalization
Leonard University of California

R01 CA35791 Role of NK Cytotoxic Factor NKCF in NK Cytotoxicity
Bonavida University of California, Los Angeles

R01 CA37063 Chemical Modification of Immunotoxin
Anderson University of New Mexico, Albuquerque

R23 CA37100 Requirements for the Membrane Transport of Immunotoxins
Donovan University of Florida

R01 CA37959 Monoclonal Antibodies to Human Melanoma Antigens
Ferrone New York Medical College

R23 CA38750 Synthetic Peptides to Induce Anti-Tumor Immunity
Smith University of Florida

R01 CA39217 Antibody-Directed Tumor Specific Chimeric Toxins
Collier Harvard University

R35 CA39838 Somatic Cell Genetics of Ig Genes
Scharff Albert Einstein College of Medicine

R01 CA40427 Ig Class-Switching and Somatic Mutations
Alt Columbia University

IMMUNOBIOLOGY OF SARCOMAS, CARCINOMAS, AND MELANOMAS (IB)

R01 CA12796 Immunogenetics of Tumor Related Alloantigens
Briles Northern Illinois University

P01 CA14489 Children's Cancer Research Center
D'Angio Children's Hospital of Philadelphia

R01 CA19754 Immunoselection and Cancer: A Problem in Evolution
Cohn Salk Institute for Biological Studies

R01 CA31336 Immunobiology of B16 Melanoma Metastasis
Stackpole New York Medical College

R01 CA32591 Regulatory Mechanisms of Neoplasia
Cerny University of Texas Medical Branch, Galveston

R01 CA37343 Autoimmune Paraneoplastic Syndromes
Lennon Mayo Foundation

R01 CA40266 Tumor Cell Recognition by Activated Macrophages
Gooding Emory University

HOST-TUMOR IMMUNOPATHOLOGY (IP)

R01 CA28139 Immunobiology of Tumor Metastases
Feldman Weizmann Institute of Science

R01 CA28332 In Situ Antitumor Immunity and Effects of Radiation
Lord University of Rochester

R01 CA30196 Immunopathology of X-Linked Lymphoproliferative Syndrome
Purtilo University of Nebraska Medical Center

R01 CA31837 Mechanisms of Carcinogenesis
Prehn Institute for Medical Research, Santa Clara County

R01 CA33119 Human Tumor-Host Relationships In Vivo
Warnke Stanford University

R23 CA36109 The Role of the Thymic Epithelium in Leukemogenesis
Tempelis Mount Sinai Medical Center (Milwaukee)

R01 CA36243 Immunopathologic Studies of Hodgkin's Disease
Ford University of Texas System Cancer Center

R01 CA39853 Tumor Progression and the Immunobiology of Metastasis
Frost University of Texas System Cancer Center

EFFECTS OF DISEASE ON IMMUNE FUNCTION (IS)

R01 CA16885 Propagation of Thymus-Derived Lymphocyte Lines
Ruddle Yale University

R01 CA18234 Immunobiology of Primary Intracranial Tumors
Roszman University of Kentucky

R01 CA20543 Antigen-Antibody Complexes in Cancer Patients' Sera
Rossen Baylor College of Medicine

R01 CA24429 Immunosuppressants and Lymphocyte Function
Winkelstein Montefiore Hospital

R01 CA26169 Immunosuppression by Avian Acute Leukemia Viruses
Bose University of Texas, Austin

R01 CA29200 Autologous Immunity to Human Melanoma
Guerry University of Pennsylvania

R01 CA30461 Clonal Analysis of Cellular Immune Response in Melanoma
Mukherji University of Connecticut Health Center

R01 CA31547 Immunosuppressive Properties of Retrovirus Protein
Olsen Ohio State University

R01 CA32275 Immunoregulation of Murine Myeloma
Lynch University of Iowa

R23 CA33012 Cellular Interactions in Hemopoiesis
Steinberg Beth Israel Hospital, Boston

R01 CA33653 Mechanism of Immune Interferon Synthesis in Thymocytes
Reem New York University

R01 CA33873 Interleukin-2 In Human Immunodeficiency Syndromes
Mertelsmann Sloan-Kettering Institute for Cancer Research

R23 CA34671 Inhibitors of Macrophages in Neoplasia Relationship
Cianciolo Duke University

U01 CA34994 Interferon and the Etiology of Acquired Immunodeficiency
Preble U.S. Uniformed Services University of Health Science

R01 CA35922 Suppressor Cells in Cancer and Immunodeficiencies
Schwartz University of Michigan at Ann Arbor

R23 CA36896 Regulation of Human Megakaryocytopoiesis
Gewirtz Temple University

R01 CA36915 Cellular Modulation of Hemopoiesis
Greenberg Stanford University

R01 CA37949 Cancer Chemotherapy and Macrophage Activation
Gudewicz Albany Medical College of Union University

R23 CA39016 Lymphokines in FELV Immunosuppression and Leukemia
Yamamoto University of California, Davis

R01 CA39068 DNA Sequencing Involved in the Heavy Chain Switch
Dunnick University of Michigan, Ann Arbor

R01 CA39201 Molecular Mechanism of NK Cell-Mediated Tumor Lysis
Podack New York Medical College

R01 CA39632 NK Cell Role in Resistance to Leukemia
Lotzova University of Texas System Cancer Center

R01 CA41699 Cell Interactions in Leukemia
Platsoucas University of Texas

IMMUNOTHERAPY: MECHANISMS RATHER THAN THERAPEUTIC RESULTS (IT)

R01 CA27625 Hybrid Tumor Cell Immunotherapy
McCune University of Rochester

R01 CA29039 Molecular Targeting of Cytotoxic Ricin A Chain
Baso Dana-Farber Cancer Institute

R01 CA30070 Carcinoma Associated Antigens and Immunoglobulins
Anderson Northwestern University

R01 CA30088 Synergy of Tumor Chemotherapy and Host Immunity
Dray University of Illinois at Chicago

R01 CA31787 Irradiation and Marrow Transplantation in Large Animals
Thomas Fred Hutchinson Cancer Research Center

R01 CA33387 Passive Immunotherapy of Spontaneous AKR Leukemia
Weinhold Duke University

R01 CA34060 Elimination of Neuroblasts from Bone Marrow with AB + C
Boyle University of Florida

R01 CA34358 Immunogenicity of a Polyvalent Melanoma Antigen Vaccine
Bystryn New York University Medical Center

R01 CA34751 Treatment of Suppressor Cell Activity in Melanoma
Livingston Sloan-Kettering Institute for Cancer Research

R01 CA39957 Mechanism of Action of Thiabendazole
Lundy Nassau Hospital

R01 CA40168 Anti-Idiotype Antibodies: Antigens for Human Tumors
Rutzky University of Texas

LYMPHOCYTES (LB)

R01 CA04946 Severe Combined Immunodeficiency
Bosma Institute for Cancer Research

P01 CA12800 Immune Functions and Cancer
Fahey University of California, Los Angeles

R01 CA12844 Controls of Proliferation Specific for Leukemias
Nakamura State University of New York at Buffalo

R01 CA14462 Properties of Lymphoid Tumor Cells In Vivo and In Vitro
Thorbecke New York University

R01 CA15334 Cellular Mechanisms in Tumor-Specific Immunity
Smith University of Florida

P01 CA15822 Immunobiology of Normal and Neoplastic Lymphocytes
Nowell University of Pennsylvania

P01 CA16673 Cell Differentiation Studies in Cancer Immunobiology
Cooper University of Alabama in Birmingham

R01 CA17733 Lymphocyte Antigens: Structure, Function and Synthesis
Trowbridge Salk Institute for Biological Studies

R01 CA19170 Mechanisms of T-Cell Mediated Suppression of Tumor Growth
Bernstein Fred Hutchinson Cancer Research Center

R01 CA19529 Cell-Mediated Immunity in Humans: Mechanisms and Uses
Valentine New York University

R01 CA20531 Genetic Analysis of Normal and Malignant Lymphocytes
Yunis Dana-Farber Cancer Institute

R01 CA20819 Phagocytic Cells: Regulation, Dysfunction and Disease
Van Epps University of New Mexico, Albuquerque

R01 CA20833 Cell-Mediated Cytotoxicity in Humans
Trinchieri Wistar Institute of Anatomy and Biology

R01 CA22241 T-Cell Development: Immunogenetics, Defects, Therapy
Boyse Sloan-Kettering Institute for Cancer Research

R01 CA22677 Pathobiology of Myeloma and Anti-Idiotypic Immunity
Schreiber University of Chicago

R01 CA22786 Receptor Dynamics and Normal/Tumor Cell Function
Bankert Roswell Park Memorial Institute

R01 CA23262 Terminal Transferase in Normal and Leukemic Lymphoid Cells
Bollum U.S. Uniformed Services Univ. of Health Sciences

R01 CA24436 Lymphocyte Receptor Function
Wofsy University of California, Berkeley

R01 CA24442 Chemical Basis for Receptor Recognition of Lysozymes
Sercarz University of California, Los Angeles

R01 CA24472 The Development of Thymocytes and Their Progeny
Basch New York University

R01 CA24607 Suppressor T Cells of Mixed Leukocyte Reaction in Man
Engleman Stanford University

R01 CA25054 Cellular Mechanisms Regulating Antibody Production
Mullen University of Missouri, Columbia

R01 CA25253 Immunoregulatory Network Probed by Cell Hybridization
Bankert Roswell Park Memorial Institute

R01 CA25369 Human Leukemia Antigens: Isolation and Characterization
Schlossman Dana-Farber Cancer Institute

R01 CA25583 Cell-Mediated Immunity in Mammary Tumor Models
Lopez University of Miami

R01 CA25612 Immunologic Effects on Tumor Growth and Rejection
Plate Rush University

R01 CA25738 T-Cell Differentiation: Molecular Mechanisms
Boyse Sloan-Kettering Institute for Cancer Research

P01 CA25803 Control of Normal and Abnormal Cell Development
Bevan Scripps Clinic and Research Foundation

R01 CA26284 Regulation of Adenosine Deaminase in Human Cells
Daddona University of Michigan at Ann Arbor

R01 CA26297 Primary Structure of MHC I Region Associated Antigens
McKean Mayo Foundation

R01 CA28708 Immunoregulation of Myeloma Cell Differentiation
Rohrer University of South Alabama

P01 CA28900 Control of Antigen-Specific T-Cell Responses
Eisen Massachusetts Institute of Technology

R01 CA28936 Immunoregulation in Autoimmunity and Malignant Disease
Haynes Duke University

P01 CA29606 Immunoregulation--T Cells and Their Products
Janeway Yale University

R01 CA31534 Isotype Switching in a Neoplastic B Cell Model, BCL1
Tucker University of Texas Health Science Center, Dallas

R01 CA31536 Investigation of Human Mitogen Induced T-Cell Colonies
Spitzer University of Texas System Cancer Center

R01 CA31685 Differentiative Programs of Lymphoid Progenitor Cells
LeBien University of Minnesota of Minneapolis-St. Paul

R01 CA32018 T Subset Interactions in Specific Tumor Immunotherapy
Perry Emory University

R01 CA32277 FC Receptor-Bearing T Lymphocytes in Murine Myeloma
Lynch University of Iowa

R01 CA32685 The Immunobiology of Human Antileukemic Lymphocytes
Sondel University of Wisconsin, Madison

R23 CA32969 Functional Studies of Transformed Natural Killer Cells
Johnson University of Nebraska Medical Center

R01 CA33005 Molecular Mechanism of Natural Cell-Mediated Cytolysis
Oeltmann Vanderbilt University

R01 CA33589 Mechanism of NK Mediated Cytolysis
Forbes Vanderbilt University

R01 CA33939 Lymphoid Cell Treatment of Leukemia
Furmanski AMC Cancer Research Center and Hospital

R01 CA34109 Helper Cells/Factors from Nonresponders
Waltenbaugh Northwestern University

R01 CA34112 Molecular Mechanisms in Cellular Immunology
Callewaert Oakland University

R01 CA34127 Antibody Variable Genes: Development and Diversity
Gearhart Johns Hopkins University

R01 CA34129 Regulation of Human and Murine Cytolytic T Lymphocytes
Burakoff Dana-Farber Cancer Institute

R01 CA34442 In Vitro Induction of NK Cytotoxicity
Golub University of California, Los Angeles

R01 CA34817 Regulation of Activity in Cloned Anti-Tumor Lymphocytes
Russell Washington University

R01 CA34899 In Vitro Analysis of Antibody Regulation in Humans
Stevens University of California, Los Angeles

U01 CA34976 Etiology and Immunological Basis of the AID Syndrome
Valentine New York University

U01 CA34981 AIDS--Mechanism of Defective Immunoregulation
Hauptman Thomas Jefferson University

R01 CA35457 Natural Killer Cell Heterogeneity and Differentiation
Tai University of New Mexico, Albuquerque

R01 CA35654 Monoclonal T-Lymphocyte Factor Regulation of Myeloma
Rohrer University of South Alabama

R01 CA35704 Mechanisms of Antigen Processing of Hemoglobin
Kazim University of New Mexico

R01 CA35730 Requirements for B-Cell IA-Alloantigen Presentation
Kubo National Jewish Hospital and Research Center

R01 CA35793 Natural Kill of HSV-1 Infected Targets: Basic Biology
Fitzgerald Sloan-Kettering Institute for Cancer Research

R01 CA35978 The Role of Gangliosides in Modulation of Mitogenesis
Merritt George Washington University

R01 CA36107 Immune Response to Modified Self and Tumor Antigens
Scott University of Rochester

R01 CA36302 T-Cell Help in B-Cell Activation, Division, and Maturation
Corley Duke University

R23 CA36403 Isotype Suppressor T Cells With FC Receptors in Myeloma
Hoover University of Pennsylvania

R01 CA36642 Helper T Cells: Comparison of T-T and T-B Interaction
Corley Duke University

R01 CA37006 Regulatory Interactions of NK Cells with B Cells
Pollack University of Washington

R01 CA37252 Myeloma Cell Heterogeneity and Immunoregulation
Kemp University of Iowa

R01 CA37344 Molecular Analysis--B Lymphocyte Activation
Raschke La Jolla Cancer Research Foundation

R01 CA37372 Tyrosine Protein Kinases and Lymphocyte Activation
Geahlen Purdue University, West Lafayette

R01 CA37374 Immunochemical Genetics of Murine Alloantigens
Michaelson Center for Blood Research

R01 CA37438 Mechanisms of B-Cell Activated Feedback Regulation
Calkins Thomas Jefferson University

R23 CA37955 Biophysical Basis of Cell Killing by CTL
Sung Columbia University

R01 CA38336 Ontogeny, Regulation and Characterization of NK/K Cells
Kim University of Health Sciences, Chicago Medical School

R01 CA38349 Significance of IR-Genes in T-Cell Mediated Suppression
Araneo University of Utah

R01 CA38350 T-Cell Influences on B-Cell Maturation
Bottomly Yale University

R01 CA38351 Ontogenetic Development of Lymphocytes
Hammerling Sloan-Kettering Institute for Cancer Research

R01 CA38352 Molecules Mediating the Attachment of Lymphocytes
Pierschbacher La Jolla Cancer Research Foundation

R01 CA38353 Modification of Regulatory T-Lymphocyte Function
Polmar Washington University

R23 CA38899 Transformed T-Cell Lines for Study of T-Cell Maturation
Jung Oklahoma Medical Research Foundation

R01 CA38942 Proteinases and Lethal Mechanism of Natural Killer Cells
Hudig University of Nevada, Reno

R01 CA39078 Analysis of Neonatal H-2 Tolerance
Streilein University of Miami

R23 CA39345 Characterization of Activated Natural Killer Cells
Golightly State University of New York, Stony Brook

R35 CA39790 Cellular Pathways Involved in Immunoregulation
Dorf Harvard Medical School

R43 CA39881 Extracorporeal Removal of Tumor Antigen
Gregonis Biomaterials International, Inc.

R01 CA39890 Effector Lymphocyte-Target Cell Interaction
Lindquist University of Connecticut Health Center

R01 CA39891 Protein Kinases, Ca^{2+}, and PI in Stimulated Lymphocytes
Mastro Pennsylvania State University Park

R43 CA39966 Chromosome Preparation System Phase I
Melnyk Medical Genetics, Inc.

R01 CA40272 Lymphocyte Homing in Normal and AIDS Affected Model
Gallatin Fred Hutchinson Cancer Research Center

R23 CA40430 Kinetic Analysis of Cytolytic Reactions
LeFever Medical College of Wisconsin

R01 CA41679 In Vitro Analogs of the Thymic Microenvironment
Keitman University of Texas

R01 CA41987 Human Natural Killer Cells: Regulation and Heterogeneity
Koren U.S. Environmental Protection Agency

R01 CA42005 Functional Analysis of T-Lymphocyte Subpopulations
Choi Alton Ochsner Medical Foundation

MONOCYTES AND MACROPHAGES (MB)

R01 CA14113 Macrophage Activation for Tumor Cell Cytotoxicity
Shin Johns Hopkins University

P01 CA14723 Study of Experimental Cancer Immunology
Benacerraf Harvard University

R01 CA16784 Tumoricidal Effects of Macrophages: Pathologic Study
Adams Duke University

R01 CA18672 The Role of Macrophage Subclasses in Tumor Immunity
Fishman St. Jude Children's Research Hospital

R01 CA20822 Cell Interaction and the Clotting System
Colvin Massachusetts General Hospital

R01 CA21225 Surface Protein GP160 in Macrophage Activation
Remold-O'Donnell Center for Blood Research

R01 CA22090 Biochemical Bases of Cytotoxicity by Phagocytes and Lymphocytes
Nathan Rockefeller University

R01 CA22105 Analysis of Mononuclear Phagocyte Differentiation
Tomasi University of New Mexico, Albuquerque

R01 CA24067 Fc Receptor Structure and Function
Anderson University of Rochester

R01 CA25052 Immune Response in Vitro H-2 (IR) Locus Function
Niederhuber University of Michigan at Ann Arbor

R01 CA26824 Mononuclear Phagocytes in Human Ovarian Carcinoma
Mantovani Mario Negri Institute Pharmacologiche

R01 CA27523 Macrophages and Tumor Growth
Evans Jackson Laboratory

P01 CA29589 Macrophage Activation: Development and Regulation
Adams Duke University

P01 CA30198 Human Mononuclear Leukocytes in Cancer
Cohn Rockefeller University

R01 CA32551 Hemopoietic Stem Cell Differentiation to Macrophages
Stanley Yeshiva University

R01 CA32898 Differentiation and Function of Human Monocytes
Trinchieri Wistar Institute of Anatomy and Biology

R01 CA33188 Macrophage Control of Normal and Leukemic Erythropoiesis
Furmanski AMC Cancer Research Center and Hospital

R01 CA34071 Macrophage Procoagulants
Shands University of Florida

R01 CA35893 A Mechanism by Which Macrophages Injure Cancer Cells
Granger Duke University

R01 CA35961 Macrophage Resistance Versus Viruses and Tumors
Morahan Medical College of Pennsylvania

R23 CA36643 Role of Complement in the Immunopathology of Macrophages
Newman University of North Carolina, Chapel Hill

R23 CA36646 Study of Fluid Pinocytosis in Stimulated Neutrophils
Davis Upstate Medical Center

R23 CA37954 Immune Functions of the Macrophage MAN/GLCNAC Receptor
Sung Oklahoma Medical Research Foundation

R01 CA38408 Effector and Suppressor Mechanisms in Tumor Immunity
Stout East Tennessee State University

R01 CA39070 Regulation of IA Gene Expression
Woodward University of Kentucky

R01 CA39093 Lymphocyte Released Cell-Toxin
Granger University of California, Irvine

R01 CA39621 Induced Macrophage Tumoricidal Activation
Hamilton Duke University

R01 CA40038 Calcium Transport in Activated Macrophages
Gorecka-Tisera Children's Hospital of Pittsburgh

R01 CA40477 Mechanism of Macrophage Recognition of Tumor Cells
Chapes Kansas State University

R01 CA41103 Immunobiology of Human Tissue Macrophages
Buckley Yale University

MALIGNANCIES OF THE IMMUNE SYSTEM (LYMPHOMA/LEUKEMIA) (MI)

R01 CA15472 Immunity and Myeloma Tumors
Eisen Massachusetts Institute of Technology

R01 CA20499 Immunobiology of Cutaneous T-Cell Lymphomas
Edelson Columbia University

R01 CA25097 Differentiation of Immune System: Cell Surface Antigens
Kersey University of Minnesota of Minneapolis-St. Paul

R01 CA26479 Immune Functions of Tumor Cell Variants
Fuji Roswell Park Memorial Institute

R01 CA31479 Proliferation and Differentiation in Human Lymphoma
Ford University of Texas System Cancer Center

R01 CA31789 Genetic-Viral-Immunologic Studies
Datta Tufts University

R23 CA31888 Monoclonal Antibodies Reactive with Human Leukemia Cells
Ball Dartmouth College

R01 CA32563 Pathogenesis of Preleukemic Aplastic Anemia
Hoover Colorado State University

R01 CA32577 Studies on Tumor Dormancy and Emergence
Wheelock Hahnemann University

R01 CA32826 Glycosphingolipids in Oncogenesis and Differentiation
Macher University of California, San Francisco

R01 CA34052 T-Cell Interactions with Cloned IA+ Accessory Cells
Kaplan University of Kentucky

R23 CA34313 Antigen Expression on Fetal and Malignant Leukocytes
Hofman University of Southern California

R01 CA34549 Role of Natural Cytotoxic Cells in Experimental Lymphoma
Ponzio University of Medicine and Dentistry of New Jersey

R01 CA34654 Immune Response and Progressive Tumor Growth
Manson Wistar Institute of Anatomy and Biology

R23 CA35463 Monoclonal Antibodies Specific for Hairy Cell Leukemia
Posnett Rockefeller University

R01 CA36776 Lymphoblastoid Receptors for Epstein-Barr Virus
Fowler University of South Alabama

R01 CA37097 Nuclear Antigen Markers in Human Blood Cells
Briggs Vanderbilt University

R01 CA38325 White Blood Cell Oxidase in Leukemia and Normal Cells
Newburger University of Massachusetts Medical School

R01 CA38663 The Immunology of Increased Aggressiveness of SJL Tumors
Lerman Wayne State University

R01 CA39492 Monoclonal Antibodies Against Leukemia
Bernstein Fred Hutchinson Cancer Research Center

IMMUNE SURVEILLANCE (SR)

R01 CA03367 Natural Resistance to Lymphoma and Marrow Transplantation
Trentin Baylor College of Medicine

R01 CA15988 Immune Surveillance and Cancer
Stutman Sloan-Kettering Institute for Cancer Research

R01 CA20408	Immunodeficiency and Tumorigenesis	
Shultz		Jackson Laboratory
R01 CA20816	Pathogenesis of Autoimmunity	
Gershwin		University of California, Davis
R01 CA20833	Cell-Mediated Cytotoxicity in Humans	
Trinchieri		Wistar Institute of Anatomy and Biology
R01 CA22517	Monocyte Function in Neoplasia	
Normann		University of Florida
R01 CA24433	Antigen Recognition by Cytotoxic Killer Cells	
Sears		University of California, Santa Barbara
R01 CA24873	Immunosuppression in Cancer Patients	
Bankhurst		University of New Mexico, Albuquerque
R01 CA25917	Cellular and Genetic Aspects of Antitumor Immunity	
Daynes		University of Utah
R01 CA26344	Autologous Lymphocyte Reactions and Immune Surveillance	
Weksler		Cornell University Medical Center
R01 CA26782	Regulation by Natural Killer Cells	
Kiessling		Caroline Institute
R01 CA27599	Genetic Control of Resistance and Immunity to P815	
Williams		Northwestern University
R01 CA28231	H-2 Associated Natural Resistance	
Carlson		Jackson Laboratory
R01 CA28834	Basophil/Mast Cell Function in the Control of Cancer	
Dvorak		Beth Israel Hospital
R01 CA29355	T-Cell Nonresponsiveness in Gross Virus-Infected Mice	
Blank		University of Pennsylvania
R01 CA30187	Regulatory Mechanisms in Human Natural Cytotoxicity	
Bloom		University of California, Los Angeles
R01 CA32553	Specific Anti-Tumor Activity by Armed Lymphoid Cells	
Pollack		University of Washington
R23 CA34302	Regulation of UV-Tumor Immunity by Cloned TS-Cell Lines	
Roberts		University of Utah
R01 CA34461	Regulation of Natural Killer Cells	
Welsh		University of Massachusetts Medical School
R01 CA34529	Oxidative Regulation of Human Natural Killer Cells	
Seaman		University of California, San Francisco

R01 CA34674 Study of Acquired Immunodeficiency and Kaposi's Sarcoma
Hersh University of Texas System Cancer Center

R01 CA35979 T-Lymphocyte Specific Genes
Storb University of Washington

R01 CA36860 Cellular Immunity to Endogenous AKR Leukemia Viruses
Green Dartmouth

R01 CA36921 Immunogenetics of Hybrid Resistance
Bennett University of Texas Health Science Center, Dallas

R01 CA36922 Immunobiology of Hybrid Resistance
Bennett University of Texas Health Science Center, Dallas

R01 CA37205 Mechanism of the NK Lethal Hit in Programmed Tumor Cells
Targan University of California, Los Angeles

R01 CA39536 Immune Mechanism in the Generation of Tumor Variants
Ghosh Roswell Park Memorial Institute

R01 CA39623 Target Cell Lysis by Cytolytic Effector Cells
Dennert University of Southern California

R01 CA39935 Genetics and Regulation of Natural Cell-Mediated Cytotoxicity
Clark University of Washington

R01 CA41972 Natural Killer Cell Target Structure and Its Receptor
Yogeeswaron Tufts University

IMMUNOTHERAPY IN ANIMAL MODELS (TA)

R01 CA11898 Brain Tumors: Immunological and Biological Studies
Bigner Duke University

R01 CA16642 Immunological Basis of Tumor Regression
North Trudeau Institute

R01 CA17818 Tumor Immunity and Tumor-Host Interactions
Stutman Sloan-Kettering Institute for Cancer Research

R01 CA27794 Mechanisms of Endotoxin-Induced Tumor Regression
North Trudeau Institute

R01 CA35299 T Cells and Their Lymphokines in Cancer Immunotherapy
Altman Scripps Clinic and Research Foundation

R01 CA37184 Antitumor Properties of Acute Inflammation
Lichtenstein University of California, Los Angeles

R01 CA38415 Evaluation of Human Melanoma Antigen as a Vaccine
Brown Oncogen

R23 CA40555 Adoptive Immunotherapy in the Mouse and Human
Eberlein Brigham and Women's Hospital

BONE MARROW TRANSPLANTATION (TT)

R01 CA20044 Transplantation Immunology
Winn Massachusetts General Hospital

R01 CA28701 Chronic Graft-Versus-Host Disease in Radiation Chimeras
Beschorner Johns Hopkins University

R01 CA29592 Active Specific Immunotherapy in Man: A Murine Model
Kahan University of Texas Health Science Center, Houston

R01 CA33794 Minor Alloantigens in Clinical Graft-Versus-Host Reaction
Elkins Children's Hospital of Philadelphia

P01 CA35048 Bone Marrow Transplantation in Leukemia
Beutler Scripps Clinic and Research Foundation

R01 CA36725 Immunotoxins in Human Bone Marrow Transplantation
Vallera University of Minnesota of Minneapolis-St. Paul

R01 CA37706 NK Cells and Bone Marrow Rejection
Dennert University of Southern California, Los Angeles

R01 CA38355 Lymphocyte Function in Normal and Chimeric Mice
Sprent Scripps Clinic and Research Foundation

R01 CA38804 Pathogenesis of Chronic Graft-Versus-Host Disease
Cramer University of Pittsburgh

R01 CA38951 Etiology and Pathogenesis of Murine Graft-Versus-Host Disease
Korngold Wistar Institute of Anatomy and Biology

R01 CA39889 Marrow Transplantation: Immune Dysfunction in GVH
Hamilton University of Washington

R01 CA40358 Cellular Pathology of Cutaenous Graft-Versus-Host Disease
Murphy Brigham and Women's Hospital

CONTRACT RESEARCH SUMMARY

Title: Resource Bank and Distribution Center for Cell Lines Useful in Research in Tumor Immunology

Principal Investigator: Dr. Anita C. Weinblatt
Performing Organization: American Type Culture Collection
City and State: Rockville, MD

Contract Number: NO1-CB-15533
Starting Date: 9/28/81 Expiration Date: 9/27/86

Goal: To provide an efficient system for the acquisition, cataloging, storage and maintenance of cell lines which are capable of long term growth in vitro and are useful in tumor immunology research. To offer to recipients expert advice on culture and characteristics of all lines shipped.

Approach: The cell lines in the bank are listed in a catalog, which is updated annually. New acquisitions are also announced in quarterly newsletters. The cell lines in the bank include, but are not limited to: B and T cell lines; lines useful in the study of macrophage/monocyte development; myelomas and their variants; cell lines useful in the study of immune effector mechanisms; and hybridomas. Lines are shipped for a fee upon request. These lines are screened for contamination with bacteria, fungi and mycoplasma; detailed characterizations are performed. Relevant lines are actively sought and persons wishing to donate lines are encouraged to contact the principal investigator or the project officer.

Progress: Cell line shipments are averaging two hundred twenty-five per month. Some of the interesting hybridomas in the bank have the following specificities: Thy-1.1; Thy 1.2; various antigens on leukocytes, red blood cells, macrophages; brain clathrin; T- and B-lymphocyte antigens including alleles of Lyt-1 and Lyt-2; immunoglobulin fragments; I-A determinants; and sheep red blood cells. Other lines of interest lines are: HUT 78 (TIB-161), a human cutaneous T cell lymphoma with properties of a mature T cell line ; and EL4.IL-2 (TIB-181), a high IL-2 (T-cell growth factor) producer. Another IL-2 producer, HUT 102 (TIB-162), also releases a unique type C retrovirus associated with T-cell lymphomas. YAC-1 (TIB-160) is a lymphoma line, which is often used as a target in NK assays. $P388D_1$ (TIB-63) secretes IL-1 and is a monocyte/macrophage line that is very popular. Two other high-demand lines are rat-mouse hybridomas M1/42.3.9.8 (TIB-126) and M1/70.15.11/2 (TIB-128). Some exciting new lines are: two hybridomas specific for murine transferrin receptor (TIB-219,220) and a hybridoma which produces IgG antibodies reacting with mouse IL-2 (TIB-222).

Significance to Cancer Research: The cell lines of the Tumor Immunology Bank are utilized by hundreds of laboratories as key tools in studies on tumor-specific antigens, antibody structure, immune-related cell functions, and cell fusions, as well as numerous other cancer-related projects.

Project Officer: Judith M. Whalen
Program: Immunology Section
FY 85 Funds: $ 0 B

Description and Introduction

The Cancer Diagnosis Research Program supports research designed to develop improved ability to identify populations at high risk, to detect cancer at earlier stages, to make more accurate diagnoses, to stage tumors more precisely for prognostic and therapeutic decisions and to monitor more effectively the changes during and following therapy. Identification of populations at high risk should result in more targeted screening programs; the development of better tests for detection and diagnosis should result in earlier detection and identification of tumors, before they become seriously invasive and/or metastatic. Improvements in detection and diagnosis are also critical for the physician in choosing the most effective therapeutic approaches.

The emphasis in diagnosis related research is on the transfer of conceptual and technological developments from basic research to the clinic. Some of the questions addressed include: How can knowledge of the process of invasion be applied to staging of tumors? Can altered metabolic products be used as markers? Can more sensitive detection methods be developed using such technologies as monoclonal antibodies and recombinant DNA? Can detection of inherited genetic polymorphisms be used to identify individuals predisposed to cancer? How can advances in engineering technology be translated into more effective diagnostic instrumentation?

Although a given research project may concentrate on a particular type of tumor or organ site, the techniques developed are often more generally applicable. Because of this, the Program has been organized into five broad disciplinary categories: Biochemistry, Immunology, Cytology, Pathology and Genetics. Biochemical diagnosis includes studies of hormones, enzymes, other proteins and metabolic products which are found in the circulation, in other biological fluids or associated with cells and which can be used to characterize tumors. Studies to develop immunological assays for identification and characterization of tumor cells and for quantitating and characterizing the host immune response are included in Immunology. Cytology research stresses the development and improvement of automated techniques for cytological evaluation. Pathology research emphasizes studies to improve methods of tumor classification, including staging and correlations with prognosis. Genetics research includes applications of the newest advances in cytogenetics and molecular genetics to cancer diagnosis. A budget summary of the Program by category is provided in the adjoining table.

The Diagnosis Research Program has recently focused significant attention on the application of genetic approaches to cancer diagnosis. This research approach is particularly timely because of breakthroughs in basic tumor biology, which indicate that specific genetic alterations are involved in tumorigenesis, and because of technological advances which facilitate the identification of these alterations in tumor tissue. The program also continues to support a considerable portfolio of research on improving applications of immunological techniques to cancer diagnosis. The following report describes recent developments in genetics and immunology as they are being applied to cancer diagnosis.

Applications of Modern Genetic Technology to Cancer Diagnosis

A tremendous effort has been made to understand the molecular mechanisms underlying the observed changes in cancer cells. The focus of much of the research has been on identification of a genetic alteration that can lead to altered regulation and ultimately to uncontrolled growth. A small number of cellular genes, proto-oncogenes, have been shown to be involved in early changes in cancer cells and subsequent alterations in their gene structure, location and/or activity can be detected. These observations and the technological developments that have allowed the basic research investigations to proceed are now being applied to cancer detection and diagnosis.

The impetus for applying genetic approaches to cancer diagnosis and detection is the result of this combination of the new understanding of oncogenes in cancer, the accumulated data associating non-random chromosomal changes with specific cancers and of several technological advances. Chromosome banding techniques have revolutionized clinical cytogenetics; recombinant DNA techniques have allowed more rapid assignment of genes to specific chromosomes and analyses of genetic alterations. Basic scientists and clinicians are collaborating in the attempt to use this new knowledge to improve patient care.

Cytogenetics as a clinical tool was quite limited until convenient and reproducible methods were found to obtain sufficient numbers of cells in metaphase and to enable clearer visualization of chromosome structure. An early breakthrough came when Nowell (1960) discovered that peripheral lymphocytes could be stimulated to dedifferentiate and divide in culture by the addition of the plant lectin phytohemagglutinin (PHA). Using this technique, the metaphase cells necessary for cytogenetic analyses could be obtained from a small amount of blood. PHA stimulation has become a standard technique for chromosome studies on peripheral lymphocytes.

But even with the ability to harvest large numbers of cells in mitosis, only limited information could be obtained. It was possible to determine whether there were extra chromosomes (such as the trisomy 21 of Down's syndrome) or missing chromosomes. Gross chromosome deletions or rearrangements could be detected, but without methods to specifically identify each chromosome, the only parameters that were assessed routinely were chromosome size and general morphology. When chromosome rearrangements resulted in new chromosomes of a similar size to other chromosomes, it was very difficult to know whether a reciprocal translocation or an inversion had occurred.

The discovery of techniques that revealed patterns unique to each pair of chromosomes meant that individual chromosomes could be identified and that a variety of alterations could be visualized. New insights into the possible etiologies of various syndromes and diseases were advanced. Caspersson and his colleagues (1970) demonstrated a consistent pattern of bright and dark bands when they applied quinacrine mustard to human chromosome preparations and observed them under a fluorescent microscope (Q-banding). The banding pattern was consistent from preparation to preparation, suggesting that a change in the pattern reflected a specific genetic alteration.

Other techniques developed to reveal reproducible banding patterns used Giemsa stain, bright field microscopy and various treatments of the chromosomes. One of the simplest and most commonly used procedures involves trypsin treatment of the chromosomes followed by Giemsa staining (G-banding; Seabright, 1971; Wang and Federoff, 1972).

Once it was apparent that significant clinical information could be gleaned from careful examination of chromosomes, efforts were made to increase the number of bands that could be distinguished on the chromosomes, i.e. the resolution. Each increase in resolution allows detection of alterations involving shorter segments of the chromosomes. Yunis' prophase banding procedure provided a method to increase the complexity of the banding pattern by staining the chromosomes when they were less condensed (Yunis, 1976; CA 31024, CA 33314).

With the development of these new banding techniques, cytogeneticists began collecting data on the association of various diseases with specific chromosome changes. It was already well established that many tumors contained abnormal chromosomes but now it became possible to define the alterations. Nowell and Hungerford (1960) had demonstrated a consistent association between the presence of an abnormally short chromosome, called the Philadelphia chromosome (Ph^1), and chronic myelogenous leukemia (CML). They originally observed that one of the two shortest chromosomes (chromosomes 21 and 22) was shorter than normal in the leukemic cells and it was assumed by many that this represented a deletion of part of the chromosome. When Rowley (1973; CA 16910) looked at banded chromosomes from CML patients, she was able to show that the Ph^1 chromosome was the result of the translocation of a piece of the long arm of chromosome 22 to another chromosome, generally to the long arm of chromosome 9. Occasionally the piece of chromosome 22 was translocated to other chromosomes. Most of the cytogenetic data associating non-random chromosome abnormalities with particular neoplasms was collected from hematopoietic and lymphoproliferative malignancies because of the relative ease of obtaining suitable metaphases from the neoplastic cells.

The solid tumors present a greater challenge because of problems in disaggregating the cells of the tumor mass, in culturing the tumor cells, in excluding the associated normal cells and in stimulating mitosis in the tumor cells to obtain metaphase chromosomes. Despite these problems, data has been collected for a few solid tumors and patterns of non-random and consistent chromosome abnormalities appear to be emerging. Early observations of neuroblastoma cells as well as other tumor cells reported the presence of double minute chromosomes (DMs), small pieces of chromosomal material not attached to chromosomes. However, an apparently more specific deletion on the short arm of chromosome 1 was demonstrated in two primary neuroblastoma tumors as well as in cell lines derived from neuroblastomas (Brodeur et al., 1977; CA 39771). Analysis of large numbers of melanoma samples has revealed some common features including anomalies associated with chromosomes 1, 5, 6, 7 and 8. A full listing of the observed chromosome abnormalities in human cancer has been compiled by Mitelman (1985).

Simultaneous with the advances in cytogenetic technology was the explosion in research on the basic molecular biology of cancer which resulted from the

breakthroughs in recombinant DNA technology. The ability to prepare nucleic acid probes to detect specific DNA or RNA sequences has allowed investigators to examine genetic alterations at the molecular level. Rowley (1977; CA 16910) observed that genes involved in nucleic acid synthesis are located on chromosomes that are often non-randomly involved in tumor cell changes. Analysis of cytogenetic data indicated that certain chromosomes (numbers 1, 8, and 14) are involved more frequently than others in cancer associated alterations (Mitelman and Levan, 1981). These kinds of observations prompted many investigators to look for associations among specific cellular activities, their genetic map locations and involvement of these loci in particular cancers. This approach formed the basis for a series of experiments with B-cell lymphomas. It was known that B-cell maturation involved recombination of separated genes for variable and constant segments of the immunoglobulin (Ig) molecule. Intervening DNA sequences were removed as the active Ig gene sequence was formed. Formation of Ig molecules is a complex process because each B-cell expresses only a single antibody type. Production of the specific antibody necessarily involves significant rearrangement of Ig gene segments in each cell. It made sense, therefore, to consider the possibility that a B-cell tumor would demonstrate a unique set of rearrangements that could be identified by a series of nucleic acid probes designed to detect Ig gene rearrangements. Ig gene rearrangements were shown to occur very early in B-cell development (Korsmeyer et al., 1981). Sklar and his colleagues (Cleary et al., 1984; CA 38621) have demonstrated that these rearrangements can be analysed and used as a diagnostic criterion for B-cell lymphoma. This disease is often difficult to diagnose but these investigators have detected Ig gene rearrangements in biopsy samples by Southern blot hybridization (a standard nucleic acid technique). They were able to distinguish lymphoma tissue from normal tissue, to detect lymphomas which did not produce immunoglobulins and to show that the Ig gene rearrangements were specific to tumors of B-cell lineage.

The implication that oncogenes are involved in tumor pathogenesis spurred efforts to determine the chromosomal locations of the known oncogenes and to search for associations between these loci and chromosomal abnormalities already known to be associated with specific cancers. Some of the results to date are as follows. The human c-*mos* and the human c-*myc* genes have been mapped to specific regions of the long arm of chromosome 8 (Neel et al., 1982). These regions have been reported to be involved in the translocation associated with several types of leukemias and lymphomas. Members of the *ras* gene family were localized by *in situ* hybridization to three chromosomal sites, one on the short arm of chromosome 11 and two on chromosome 12 (Jhanwar et al., 1983); these sites have been shown to be involved in abnormalities seen in a variety of tumors. Three other oncogenes, *abl*, *sis* and *fes*, have been mapped to chromosomes 9, 22 and 15 respectively (Jhanwar et al., 1984). Again, the locations of these oncogenes are at or near sites of translocations associated with specific tumors, e.g. the *abl* gene on chromosome 9 is located at the breakpoint where the Ph^1 translocation of a piece of chromosome 22 occurs in chronic myelogenous leukemia.

The observed coincidence between the locations of certain oncogenes and the locations of non-random chromosomal abnormalities suggested that an alteration such as a translocation might result in altered regulation of

the oncogene or other nearby genes and that such genetic activities could be detected and used diagnostically. Chromosome 8 is involved in all the observed translocations in Burkitt lymphoma cell lines and deregulation of the c-myc gene located on chromosome 8 is also seen in these lines (Emanuel et al., 1984; CA 39926). A possible new oncogene, bcl-1, was found when Ig gene probes were used to clone chromosomal sequences in B-cell lymphomas and leukemias with 11;14 translocations (Tsujimoto et al., 1984); the bcl-1 appears to be activated when translocation takes place.

Several groups are attempting to apply the new molecular techniques to the diagnosis and prognosis of CML and other related hematologic malignancies. Gale and his colleagues (CA 38569) have found a novel messenger RNA (m-RNA) transcript of c-abl in patients with CML who have the Ph^1 chromosome but not in patients with other leukemias nor in patients with a variant CML who do not have the Ph^1. They are studying the relationship between the presence of the c-abl transcript, the phase of the disease (chronic or acute) and the response to treatment. Similar questions are being addressed by Collins (CA 40728) who plans to perfect a diagnostic and prognostic test using a DNA probe prepared from the novel abl m-RNA transcript. A different approach to CML diagnosis is being used by Witte (CA 40957) who has observed that the Ph^1 translocation results in production of a novel abl protein, called p210. In addition to examining the gene structure and m-RNA production, Witte will prepare specific antisera to evaluate whether there are differences in production of the p210 protein correlated with the phases of the disease and whether such correlations can be useful in diagnosis and prognosis.

Aberrant oncogene activity in tumors can be expressed in a number of ways. One mechanism is gene amplification, the production of multiple copies of the DNA sequence of the gene. Such amplification has been observed in a variety of tumors. Brodeur et al. (1984; CA 39771) demonstrated genomic amplification of N-myc in cell lines from neuroblastomas and also in biopsy samples from untreated cases. The extent of amplification correlated with the disease stage, i.e. 0 of 15 patients with stage 1 or 2 disease showed amplification whereas 24 of 48 cases with stage 3 or 4 had amplified N-myc. The extent of amplification also varied, showing a bimodal distribution with 100-300 fold amplification in 12 cases and 3-10 fold in others. Amplified N-myc sequences have also been demonstrated in 2 of 10 retinoblastoma tumors, another human tumor of neural origin (Lee et al., 1984).

Cytogenetic data have shown that amplified genes are found in chromosomal regions called homogeneously staining regions (HSRs) and in double minute chromosomes (DMs). Amplified N-myc sequences have been localized to both HSRs and DMs in neuroblastomas.

Another type of altered activity of oncogenes can be detected as a change in the level of expression of the genes. Seeger (CA 22794) is looking at altered expression in neuroblastomas by assaying transcription of N-myc and production of N-myc protein. He will correlate these factors with disease progression to assess whether such measurements will be useful in determining prognosis.

The analysis of oncogene activation, expression and mutation is currently such an active field of research that new data are appearing daily. This

review has focused on only a few examples of studies specifically aimed at applying some of the new genetic observations and molecular techniques to diagnosis and prognosis; it is in no sense an attempt to provide a comprehensive review of the current state of knowledge.

The use of cytogenetics to determine predisposition to cancer is another area of research which has begun to benefit from the technical advances described. The Diagnosis Program issued a request for research grant applications to study cytogenetics and predisposition to cancer. These studies can be pursued at this time because of the ability to consistently identify cytogenetic abnormalities using the high resolution banding techniques. When lymphocytes or skin fibroblasts from healthy individuals are cultured in special media lacking particular nutrients, a small percentage of cells may exhibit abnormal chromosomes, i.e. chromosomes that appear to be broken at identifiable sites, called fragile sites. Extensive analyses are being performed to determine whether the presence of these sites, which often appear to coincide with cancer breakpoints, predispose individuals to specific cancers. Yunis (1983; CA 31024, CA 33314) is looking at normal lymphocytes from patients with leukemia or lymphomas and from members of their families to determine whether there is a correlation between the presence of particular fragile sites and the incidence of these cancers.

It is also possible to correlate cytogenetic observations with molecular genetic findings. The cytogenetic observation often provides the first clue to the possible involvement of genes in a particular chromosomal region. For example, a constitutional deletion (i.e. a deletion found in all of an individual's cells) on chromosome 13 was found to be associated with a small percentage of cases of retinoblastoma (Knudson, 1978; Yunis and Ramsey, 1978; CA 31024, CA 33314). Molecular analysis of retinoblastoma tumor DNA revealed that a small deletion on chromosome 13 was, in fact, necessary for the expression of the disease (Sparkes et al., 1983; Benedict et al., 1983) and provided an explanation of anomalous findings related to the pattern of heredity and disease expression. It has now been shown that the deletion in one chromosome 13 predisposes the cell to tumor formation but that deletion of the same region of the second chromosome 13 may be necessary for tumor development. A similar picture involving chromosome 11 is emerging for another childhood tumor, Wilm's tumor of the kidney.

The advances in our understanding of the molecular basis of tumor development are exciting both for the insights they provide about cellular and molecular regulation and perhaps equally for their application to improved detection, diagnosis and prognosis. Cytogenetic analyses of hematologic malignancies are increasingly becoming a critical element in the diagnostic workup. There have always been a proportion of cases for any given type of cancer which were difficult to classify and which did not appear to respond normally to therapy. Identification of specific chromosomal alterations has allowed these cases to be classified more precisely and has become an important criterion in the choice of therapy. The cataloguing of molecular alterations adds yet another dimension to the diagnosis of cancer. With appropriate nucleic acid probes, biopsy samples can be rapidly assayed for specific changes in gene structure or expression. As correlations between observed changes and disease progression accumulate, more useful diagnostic information

will emerge. The cytogenetic and molecular approaches complement each other. Sometimes, the initial observation of a chromosomal rearrangement by cytogenetic techniques suggests which genes may be involved or which probes should be used to further explore the genetic changes. The use of molecular probes allows the demonstration of submicroscopic rearrangements or alterations of specific genetic sequences. These two approaches can be expected to continue to make significant contributions to the field of cancer diagnosis.

Applications of Monoclonal Antibodies to Cancer Diagnosis

The use of antibodies for the diagnosis and treatment of cancer, like most major scientific advances, did not arise suddenly, but grew instead out of a considerable body of preliminary work. One of the earliest recorded attempts to use antibodies for the treatment of cancer dates to 1895 when Hericourt and Richet (1895 a,b) published promising studies on the efficacy of antisera to osteogenic sarcoma in the treatment of a variety of neoplasms. The diagnostic use of radioactively labeled antibodies grew out of the pioneering work of Pressman (1948; Pressman and Keighley, 1949) and of Bale et al. (1955, 1957) who demonstrated that labeled antibodies retained their ability to localize on specific tissue, including tumor tissue. Prior to the development of monoclonal antibodies, a number of other groups had shown that labeled antibodies localized on tumor tissue both *in vitro* and *in vivo* (Mahaley, 1965; Primas, 1973; Mach, 1974).

A major advance in the use of antibodies for cancer diagnosis occurred when Kohler and Milstein (1975) described a method for immortalizing antibody producing cells. Prior to this development of "monoclonal antibody" techniques, production of antisera was a cumbersome process that involved induction of antibodies in animals, collection and concentration of antibody and finally removal of unwanted components from the reagent. This resulted, at best, in mixtures of antibodies to different epitopes (structural components of the antigen that react with antibody) that were never fully satisfactory. The development of a technique that allowed selection of a specific antibody producing cell, which when grown in culture or intraperitoneally in an animal would secrete almost unlimited quantities of a specific antibody, created revolutionary opportunities in all areas of biological science. Monoclonal antibodies can be produced that react to very specific antigenic epitopes. This specificity is the reason that monoclonal antibodies have become such a powerful tool for studies in immunology, tumor biology and cancer diagnosis. Monoclonal antibodies were rapidly applied to the search for cancer specific antigens, creating a renewed interest in immunologic approaches to cancer diagnosis, prognosis and monitoring of therapy.

The hybridoma technique of Kohler and Milstein has developed rapidly over the past 10 years. However, progress remains to be made in several key areas. The ability to produce monoclonal antibodies efficiently is an important first step in the development of new antibody reagents for immunodiagnosis. There is a need to develop approaches for improving the efficiency of, or eliminating entirely, the cell fusion techniques necessary for hybridoma production. Another important area is the development of human monoclonal antibodies. Most currently available monoclonal antibodies are of mouse origin and stimulate induction of anti-mouse antibodies when injected into humans. While

anti-mouse antibodies have not been shown to pose a risk to patients, they do reduce the efficacy and specificity of the mouse reagents. The final area to be discussed in this section is that of the preparation of immunoglobulin fragments so that they retain their reactive portions but not most of their antigenic portions.

Three new approaches promise to improve or even eliminate the cell fusion techniques used in current approaches to monoclonal antibody production (Van Brunt, 1985). The Zimmerman electrofusion system uses a combination of AC and DC electric currents to first orient and then to fuse cells. This system is reported to substantially increase the number of fusions with success rates of 15 to 50%, but the resulting hybridomas may not grow efficiently. The second system, the NOVA/Hopkins avidin-biotin bridge technique, uses the bridge to hold myeloma and B-cell pairs in alignment while a short pulse of high voltage electricity fuses them. While this technique is too new to be fully evaluated, if it really succeeds, it promises to be an important technology. A third method avoids entirely the need to use myeloma cells to provide B-cells (antibody producing lymphocytes) with immortality. Instead, a cloned oncogene (myc) is inserted into a plasmid which is used to transfect lymphocytes. This methodology promises not only to increase the number of potential antibody producing cell lines, but also to solve one major problem with production of human antibodies, the lack of a suitable human myeloma cell line.

Progress in producing human-human hybridomas has been slow. The first human-human hybridoma was produced in 1980 by Olsson & Kaplin (1980). Since that time continuation of this work by Teng (CA 36422) and Olsson (CA 35227) has resulted in improved cloning efficiency, and antibody production has been increased by a factor of 10 in one case (Bron, 1984). Advances in this area have been slowed by two major problems, the lack of suitable human myeloma cell lines and the slow growth of the resulting hybridomas. Efforts to overcome these problems are continuing, (Bernier, CA 33425; Olsson, CA 35227; Heitzmann, CA 36310; Volsky, CA 36320; Teng, CA 36422; Epstein, CA 40608). In addition, as discussed earlier, application of molecular genetic techniques may obviate the need for a suitable myeloma line if transfection techniques can be utilized to produce transformed human B-cells (Van Brunt, 1985).

The IgG immunoglobulin, (one type of antibody molecule) has two segments which contain antigen specificity (variable regions) and a tail which lacks antigen specificity (the constant region). The tail of the antibody can be removed to yield either one fragment which contains both antigen specific portions ($F(ab)_2$) or two fragments (Fab) when the two antigen specific portions are separated. A recent report indicates that $F(ab)_2$ fragments can be created with two different antigen specificities by joining Fab fragments from two different monoclonal antibodies (Brennan et al., 1985). Bispecific antibodies have many potential uses for application in immunodiagnostic assays.

The use of Fab and $F(ab)_2$ fragments greatly reduces the antigenicity of the antibody preparation, which is important when non-human antibodies are used in human diagnosis or therapy. Fragment preparations have been used successfully for diagnostic imaging by Larson (1985) and Nelp (CA 29639) who used Fab specific to melanoma and by Moldofsky et al. (1984) who used $F(ab)_2$ specific to metastatic colon carcinoma.

A number of immunologic approaches are available for application to cancer diagnosis. Broadly these can be divided into assays for circulating antigens in body fluids and assays for cell associated antigens. Some assays for antigen in fluids include radioimmunoassay (RIA), enzyme immunoassay (EIA) and enzyme-linked immunosorbent assay (ELISA). Assays for cell associated antigens include radioautography using radioisotope labeled antibody, nuclear imaging, immunofluorescence and immunoperoxidase techniques. Advances in immunohistochemical methodology, notably the development of the avidin-biotin complex (ABC) method of Hsu (1981), have improved sensitivities, making them comparable to the highly sensitive radioimmunoassay methods used for measuring circulating antigens. These advances have led to increased application of immunohistochemistry in both routine and experimental pathology (Sheibani et al., 1984; Falini and Taylor, 1983).

A considerable effort has been devoted to elucidation of tumor-specific markers in the 10 years since the development of monoclonal antibodies. Most of this effort has been directed toward detecting circulating antigens and utilizing them in cancer diagnosis. Despite intense efforts and the evaluation of literally hundreds of potential cancer related antigens, only a handful of these has been identified as useful markers and none has been shown to be truly tumor specific. Recently, 42 reported ovarian tumor marker studies were evaluated by Umbach (1984) who found considerable variability in sensitivity and specificity both for different antigenic markers and for different assays to the same antigenic marker. Despite the limited success in identifying tumor specific markers, some circulating markers such as carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), human chorionic gonadotropin, and prostatic acid phosphatase have been successfully used to monitor recurrence and response to therapy (Laurence, 1983). Nonetheless, the search for circulating tumor-specific antigens will continue, as will the development of faster, more specific and more sensitive monoclonal assays for their detection.

The use of radioimmunoassay for the detection of circulating tumor associated antigens has benefited from the development of solid phase assays which permit the simultaneous assay of a large number of samples. A monoclonal antibody (C50) based solid phase RIA assay for various types of carcinoma provides one example (Holmgren et al., 1984) in which increased CA50 antigen was detected in 60% of patients with disease and was absent in 99% of those without disease.

Gupta and Morton (1984; CA 30019) have reported the development of an RIA useful in characterizing a melanoma associated circulating antigen. This group has also reported an assay for sarcoma associated antigens which detected 96% (24/25) of the patients who developed cancer following apparently successful surgical treatment, while 92% (23/25) of the patients who remained disease free showed no evidence of sarcoma antigens at last followup (Huth et al., 1984).

Recently, the focus of the search for tumor specific markers has shifted from circulating markers to cell associated markers. In part, this shift is related to the limited success in defining specific circulating markers and in part to the development of increasingly sensitive techniques in immunohistochemistry. The major disadvantage of this approach to cancer diagnosis

is that it requires a tissue sample. However, this may not be a serious drawback, since biopsy pathology is the definitive method of cancer diagnosis. A number of groups have recently reported the use of immunohistochemistry to detect cellular antigens in both fixed and unfixed tissues.

Cuttitta et al. (1984) have outlined the role of lung cancer selective monoclonal antibodies in cancer diagnosis and the use of immunhistochemistry in assessing the potential of new monoclonal antibodies as tools in diagnostic pathology.

A number of groups have applied immunohistochemical techniques to the detection of prostatic cancer (Yam et al., 1983; Wright et al., 1983). Lam and his group (CA 36934) are continuing studies in which they detected prostatic acid phosphatase (PAP) in paraffin embedded tissues from metastatic tumors. These findings led clinicians to look for and discover previously undiagnosed primary prostate tumors in each of nine patients studied. Starling et al. (CA 27623) have used immunohistochemical techniques to test a number of monoclonal antibodies to prostatic tumor cellular antigens and have identified some antibodies with potential clinical applicability (Wright et al., 1983). They have recently identified two new antibodies, TURP-27 and TURP-73, which appear even more promising for use in a panel including monoclonal antibodies to PAP and to prostate (specific) antigen for classification of prostatic adenocarcinoma. TURP-27 appears to be specific for primary and metastatic prostatic adenocarcinoma and for benign hyperplasia, but not for normal prostate. Lloyd (1983; CA 34039) has used immunohistochemistry to evaluate a number of monoclonal antibodies to ovarian carcinoma and this group has recently reported 5 monoclonal antibodies which may provide an initial panel for the immunohistochemical analysis of ovarian carcinoma. (Cordon-Cardo et al., 1985).

Nearly all cells contain a complex network of cytoplasmic filaments. This network, the cytoskeleton, appears to play a role in maintenance of cell shape and in cellular motility and intracellular organelle movement. The three major elements of the cytoskeleton can be differentiated based on their appearance in electron micrographs into microfilaments, intermediate filaments and microtubules. Microfilaments are 5 to 6 nm thick filaments which are mostly, but not exclusively, found in muscle cells, often in bundles, and have been shown to react with antibodies to actin. Microtubules are much thicker filaments (20 - 25 nm) that react with antibodies to tubulin. Both actin and tubulin are widely distributed among cell types and their presence cannot be used to distinguish one cell type from another. The intermediate filaments are intermediate in thickness (about 10 nm) between the microfilaments and the microtubules. They are novel, not only because they constitute a major part of the cytoskeleton, but also because they share many biochemical and biophysical features not found in other cytoplasmic constituents. Intermediate filaments are extremely tough and difficult to dissolve, even in nonionic detergents (Virtanen et al., 1983; Gown and Gabbiani, 1984; CA 28238). Most important to their utilization in cancer diagnosis is the finding that different cell types appear to express unique subclasses of intermediate filaments which can be distinguished on the basis of both their biochemical and antigenic properties. Moreover, these distinctions are generally present in cancer tissue as well as in normal tissues of the same origin.

The intermediate filaments include five major classes:

1) The cytokeratins are a family of proteins associated with epithelial cells. Antibodies to these intermediate filaments have been widely demonstrated to be highly specific for carcinoma, a cancer of epithelial origin, and therefore useful in distinguishing it from other types of malignancy.

2) Vimentin, is a single protein which is present in all mesenchymal cells. Its presence can serve to distinguish cancers of mesenchymal origin (sarcomas, lymphomas, etc.) from carcinomas.

3) Desmin is a protein which is apparently closely related to vimentin, differing in only a few amino acids, but which is nearly always found in muscle cells. Antibodies to desmin are reactive with myogenic sarcomas.

4) Neurofilaments are a family of three proteins (the neurofilament triplet) which are associated with neural processes and cell bodies. Neurofilaments have been demonstrated in well-differentiated neural tumors (ganglioneuroblastoma, pheochromocytoma, esthesioneuroblastomas), but not consistently in poorly differentiated tumors such as neuroblastoma.

5) Glial Fibrillary Acidic Protein (GFAP) is a protein which is found in astrocytes and ependyma.

The utility of antibodies directed against intermediate filaments in cancer diagnosis, particularly differential diagnosis of neoplasms with similar morphology, has been extensively studied in the past few years. Most of this effort has concentrated on the cytokeratins, both because of their association with cells of epithelial derivation and because they represent the largest family of intermediate filament proteins. More than 19 different cytokeratin proteins have been identified, and their distribution in groups of two to ten within specific epithelial subtypes suggests their potential application in the identification and classification of various carcinomas.

Sun and his colleagues have studied the cytokeratin family extensively (Cooper et al., 1985). Individually and in combination, the monoclonal antibodies to cytokeratin subfamily proteins allow differentiation of carcinomas based on their cellular nature. Monoclonal antibodies have been developed which react with nearly all cytokeratins, while other antibodies have been developed that only react with specific cytokeratin subclasses. Gown and Vogel (1984; CA 28238) have produced antibody specific for nonsquamous epithelium, primarily for squamous epithelium, and for the suprabasal portions of squamous epithelium. Debus et al. (1984) have produced antibody specific for simple epithelium.

The use of antibodies that react with nearly all cytokeratins allows differentiation of carcinomas from tumors of other origin. This ability to identify carcinomas can be particularly important in resolving questions which arise in the 5-10% of tumors which present diagnostic difficulties in routine pathology. Examples include discrimination of poorly differentiated carcinoma from lymphoma, sarcoma or melanoma; metastatic carcinoma in the CNS from primary glioma; spindle cell carcinoma from sarcoma; and evaluation

›f small round cell tumors of childhood. Reaction with specific cytokeratins ay be useful in subclassifying carcinomas and in identifying the cellular ›rigin of metastatic tumors.

The other classes of intermediate filaments are less complex than the cytokeratins. The neurofilament triplet proteins are distributed in the same ratio throughout central and peripheral neurons, with minor exceptions (Virtanen et al., 1983). Trojanowski et al. (CA 36245) have demonstrated the presence of neurofilaments in a number of differentiated neuronal tumors, while Osborn and Weber (1983) have reported detection of neurofilaments in ganglioblastoma and pheochromocytoma. They have also reported that neurofilaments were detected in neuroblastoma frozen sections, but not in alcohol-fixed paraffin embedded sections, but with too few samples to allow generalization of these results.

The remaining intermediate filament classes (vimentin, desmin and GFAP) are single proteins which are apparently not divisible into subfamilies. Vimentin and desmin, as discussed previously, are characteristic of mesenchymal cells, with desmin generally restricted to muscle cells. GFAP is present in glial cells and is generally present in ependymal cells. The presence of GFAP has been demonstrated in glioma, astrocytoma, gliosarcoma, and subependymoma. Sympathetic ganglion tumors, of central nervous system origin, generally lack GFAP, but at least some including ganglioneuroblastoma and pheochromocytomas have been shown to contain neurofilaments (Osborn and Weber, 1983).

Panels of monoclonal antibodies that react with each class of intermediate filaments (at least one of which is commercially available) also show promise in the differential diagnosis of malignant neoplasms. A very important application is the demonstration that squamous cell carcinoma could be be differentiated from adenocarcinoma in peritoneal and pleural effusions and in fine needle aspirates from palpable lymph nodes using a panel of monoclonal antibodies (Ramackers, 1984). This technique and its obvious variants promises an effective means of differential diagnosis in cases where routine cytologic techniques cannot be utilized. The number and the clinical utility of assays for immunocytochemical detection of intermediate filaments should be expected to increase with the commercial availablity of panels of monoclonal antibodies to the major classes of intermediate filaments.

The development of monoclonal antibody techniques for specific in vivo localization of radionuclides and other labels in tumor tissues may revolutionize many aspects of cancer biology. Recent advances in a number of areas, particularly molecular genetics, hybridoma technology, radiochemistry and the molecular biology of cell receptors promise rapid progress in the next decade. Current problems include difficulty in identifying appropriate antibodies, selecting the most appropriate labels, effectively labeling the antibodies and selecting the most effective routes of administration (Keenan, 1985).

Clinical and laboratory studies continue to demonstrate the increased applicability of radioimmunodetection techniques in cancer diagnosis. Goldenberg et al. (CA 37407) pioneered these techniques with I-131 labeled CEA antibodies and alpha-fetoprotein antibodies. Studies by this group are

continuing and are now supported by an Outstanding Investigator Grant (CA 39841). Other investigators have utilized human chorionic gonadotropin, prostatic acid phosphatase and anti-renal cell antibodies (Bagshawe et al., 1980; Papsidero et al., 1980; Ghose et al., 1980). The work with Fab fragments in the diagnosis and treatment of melanoma is continuing, both by Larson, now at the NIH (Larson, 1985) and by Nelp (CA 29639), at the University of Washington. Brown et al. (1985; CA 35354) have developed a monoclonal antibody to a human malignant fibrous histiocytoma and have demonstrated its possible utility in localization of both locally recurrent and malignant sarcoma tumors in patients. Espenetos et al. (1984) have demonstrated the potential utility of I-123 labeled monoclonal antibodies to ovarian carcinoma after intravenous administration.

The ten years since the development of monoclonal antibodies have been years of revolution in many areas of biology. The application of these techniques to cancer diagnosis, detection and monitoring of therapy has been productive, but there is reason to believe that advances of equal or greater importance will be made in the next ten years. In this section we have detailed research efforts to identify cell associated antigens which may serve as tumor markers or be useful in the identification and classification of tumors. The use of intermediate filaments and the development of other specific immunohistochemical assays using monoclonal antibody reagents appears particularly promising, as does the development of in vivo techniques for localizing tumors, using radioactive or other labels, in humans.

Discussion

The Diagnosis Research Program has increased its grants portfolio by about thirty percent in the last year. This reflects both an increase in the number of applications for support of diagnosis related research projects as well as an increase in the number of reviewed applications that fall into the fundable range. Most of the new grants are in the Genetics and Pathology categories, indicating that these are areas of new and renewed interest within the biomedical research community.

The new interest in application of genetic approaches to cancer detection, diagnosis and prognosis comes as a result of advances in technology. The ability to identify genetic alterations by both cytogenetic and molecular techniques makes possible the correlation between the observed alterations and specific diseases. In addition, it is possible that more precise information can be obtained regarding disease classification and staging. Such information is critical for the clinician in making decisions about therapeutic regimes.

Improvements in hybridoma technology have spurred the production of a tremendous range of monoclonal antibodies. These antibodies are being tested for their utility in identifying tumor antigens and for their ability to distinguish between normal and neoplastic tissue as well as among neoplastic cells of different tissue origin. Because of the increased specificity afforded by monoclonal antibodies, there has been renewed interest in immunodiagnostic approaches, especially as applied to immunohistochemistry. As described in this year's report, new antibodies and improved techniques for visualizing

the antigen-antibody reactions are being used to refine pathological classification to provide clinicians with more complete information about the nature of the tumor.

It is anticipated that the results of the research described here will have an impact on other areas of diagnosis research as well. For example, both nucleic acid probes and monoclonal antibodies are being used to obtain more information from flow cytometry by allowing more precise analysis of the population of cells contained in a given tumor. New tumor associated antigens are being isolated and characterized by using monoclonal antibodies in purification procedures. This increased activity in cancer diagnosis research is expected to continue and the Diagnosis Research Program will continue to encourage research on the application of new technologies to diagnosis.

TABLE

CANCER DIAGNOSIS BRANCH

ALL PROJECT EFFECTIVE DURING FISCAL YEAR 1985

Number	Category	Grants		Contracts	
		Number	Current Funding (in Thousands)	Number	Current Funding (in Thousands)
1.	Biochemistry	22	$ 3,117	0	0
2.	Immunodiagnosis	46	5,617	0	0
3.	Cytology	23	4,021	0	0
4.	Pathology	14	1,432	0	0
5.	Genetics	14	1,775	0	0
6.	Contracts Resource/Research	0	0	7	1,763
7.	Small Business Innovative Research	14	892	0	0
	TOTALS	133	16,854	7	1,763

REFERENCES

Bagshawe, K.D., Searle, F., Lewis, J., Brown, P., and Keep, P. Preliminary Therapeutic Localization Studies with Human Chorionic Gonadotropin. Cancer Res. 40:3016-3017, 1980.

Bale, W.F. and Spar, I.L. Studies Directed Toward the Use of Antibodies as Carriers of Radioactivity for Therapy. Adv. Biol. Med. Physics 5: 285-356, 1957.

Bale, W.F., Spar, I.L., Goodland, R.L. and Wolfe, D.E. In Vivo and In Vitro Studies of Labeled Antibodies Against Rat Kidney and Walker Carcinoma. Proc. Soc. Exp. Biol. Med. 89:564-568, 1955.

Benedict, W.F., Murphree, A.L., Banerjee, A., Spinna, C.A., Sparkes, M.C., and Sparkes, R.S. Patient with 13 Chromosome Deletion: Evidence that the Retinoblastoma Gene is a Recessive Cancer Gene. Science 219: 973-975, 1983.

Brennan, M., Davison, P.F., and Paulas, H. Preparation of Bispecific Antibodies by Chemical Recombination of Monoclonal Immunoglobin G Fragments. Science 229:81-83, 1985.

Brodeur, G.M., Seeger, R.C., Schwab, M., Varmus, H.E., and Bishop, J.M. Amplification of N-myc in Untreated Human Neuroblastomas Correlates with Advanced Disease Stage. Science 224:1121-1124, 1984.

Brodeur, G.M., Sekhon, G.L., and Goldstein, M.N. Chromosomal Aberrations in Human Neuroblastomas. Cancer 40:2256-2263, 1977.

Bron, D., Feinberg, M.B., Teng, N.N., and Kaplin, H. Production of Human Monoclonal IgG Antibodies Against Rhesus (D) Antigen. Proc. Natl. Acad. Sci. U.S.A. 81:3214-3217, 1984.

Brown, J.M., Greager, J.A., and Das Gupta, T.K. Characterization of a Sarcoma-Associated Antigen Using Monoclonal Antibodies. Proceedings of A.A.C.R. 26:313, 1985.

Caspersson, T., Zech, L., and Johanson, C. Differential Banding of Alkylating Fluorochromes in Human Chromosomes. Exp. Cell Res. 60:315-319, 1970.

Cleary, M.L., Chao, J., Warnke, R., and Sklar, J. Immunoglobulin Gene Rearrangement as a Diagnostic Criterion of B-Cell Lymphoma. Proc. Nat'l Acad Sci U.S.A. 81:593-597, 1984.

Cooper, D., Schermer, A., and Sun, T.T. Biology of Disease: Classification of Human Epithelia and Their Neoplasms Using Monoclonal Antibodies to Keratins: Strategies, Applications and Limitations. Lab. Invest. 52:243-256, 1985.

Cordon-Cardo, C., Mattes, M.J., Melamed, M.R., Lewis, J.L. Jr., Old, L.J., and Lloyd, K.O. Immunopathologic Analysis of a Panel of Mouse Monoclonal Antibodies Reacting with Human Ovarian Carcinomas and Other Human Tumors. Int. J. Gyn. Pathol. 4:121-130, 1985.

Cuttitta, F., Rosen, S., Fedorko, J., Gregorio, T., Stephenson, S., Mulshine, J., Carney, D.N., Fargion, S., Abrams, P.G., Moody, T.W., Gazdar, A.F., and Minna, J.D. Monoclonal Antibodies to Human Lung Tumor Antigens. in Monoclonal Antibodies and Cancer, George Wright, Jr., ed., Marcel Dekker, Inc., New York, 1984.

Debus, E., Moll, R., Franke, W.W., Weber K., and Osborn, M. Immunohistochemical Distinction of Human Carcinomas by Cytokeratin Typing with Monoclonal Antibodies. Am. J. Pathol. 114:121-130, 1984.

Emanuel, B.S., Selden, J.R., Chaganti, R.S.K., Jhanwar, S., Nowell, P.C. and Croce, C.M. The 2p Breakpoint of a 2;8 Translocation in Burkitt Lymphoma Interrupts the V_k Locus. Proc. Nat'l Acad. Sci. U.S.A. 81:2444-2446, 1984.

Espenetos, A.A., Shepard, J., Britton, K.E., Hawkins, L., Nimmon, C.C., Taylor-Papadimitriou, J., Durbin, H., Malpas, J.S., Mather, S., Granowska, M., Duke, D., and Bodmer, W.F. Radioimmunodiagnosis of Ovarian Cancer Using ^{123}I Labelled Tumor Associated Monoclonal Antibodies. Cancer Detection and Prevention 7:45-49, 1984.

Falini, B. and Taylor C.R. New Developments in Immunoperoxidase Techniques and Their Application. Arch. Pathol. Lab. Med. 107: 105-117, 1983.

Ghose, T., Norvell, S.T., Aquino, J., Belitsky, P., Tai, J., Guclu, A., and Blair, A.H. Localization of ^{131}I - Labeled Antibodies in Human Renal Cell Carcinomas and in a Mouse Hepatoma and Correlations with Tumor Detection by Photoscanning. Cancer Res. 40:3018-3031, 1980.

Gown, A. and Gabbiani, G. Intermediate sized (10nm) Filaments in Human Tumors. Chapter 5 in Advances in Immunohistochemistry, DeLellis, R.A.,ed., Masson, New York. pp. 89-109, 1984.

Gown, A.M. and Vogal, A.M. Monoclonal Antibodies to Human Intermediate Filament Proteins II. Distribution of Filament Proteins in Normal Human Tissues. Am. J. Pathol. 114:309-321, 1984.

Gupta, R.K. and Morton, D. Studies of a Melanoma Tumor-Associated Antigen Detected in the Spent Culture Medium of a Human Melanoma Cell Line by Allogenic Antibody. I. Purification and Development of a Radioimmunoassay. J.N.C.I. 72:67-74, 1984.

Hericourt, J. and Richet, C. Traitement d'un cas de Sarcome par la Serotherapie. C. R. Hebd. Seances Acad. Sci. 120:948-950, 1895 a.

Hericourt, J. and Richet, C. De la Serotherapie dans le Traitement du Cancer. C. R. Hebd. Seances Acad. Sci. 121:567-569, 1895 b.

Holmgren, J., Lindholm, L., Persson, B., Lagergard, T., Nilsson, D., Svennerholm, L., Rudenstam, C-M., Unsgaard, B., Yngvason, F., Pettersson, S., and Killander, A. Detection by Monoclonal Antibody of Carbohydrate Antigen CA50 in Serum of Patients with Carcinoma. Brit. Med. J. 288: 1479-1482, 1984.

Hsu, S-M., Raine, L., and Fanger, H. Use of Avidin-Biotin Peroxidase Complex (ABC) in Immunoperoxidase Techniques: A Comparison Between ABC and Unlabeled Antibody (PAP) Procedures. J. Histochem. Cytochem. 29:577-590, 1981.

Huth, J.F., Gupta, R.K., Eilber, F.R., and Morton, D.L. A Prospective Postoperative Evaluation of Urinary Tumor-Associated Antigens in Sarcoma Patients: Correlation with Disease Recurrence. Cancer 53:1306-1310, 1984.

Jhanwar, S.C., Neel, B.G., Hayward, W.S., and Chaganti, R.S.K. Localization of the Cellular Oncogenes abl, sis, and fes on Human Germ-Line Chromosomes, Cytogenet. Cell Genet. 38:73-75, 1984.

Jhanwar, S.C., Neel, B.G., Hayward, W.S., and Chaganti, R.S.K. Localization of c-ras Oncogene Family on Human Germ-Line Chromosomes. Proc. Nat'l Acad. Sci. U.S.A. 80:4794-4797, 1983.

Keenan, A., Harbert, J. C., and Larson, S. M. Monoclonal Antibodies in Nuclear Medicine. J. Nucl. Med. 26:531-537, 1985.

Knudson, A. G. Retinoblastoma: A Prototypic Hereditary Neoplasm. Semin. Oncol. 5:57-60, 1978.

Kohler, G. and Milstein, C. Continuous Cultures of Fused Cells Secreting Antibody of Predefined Specificity. Nature 256:495-497, 1975.

Korsmeyer, S.J., Hieter, P.A., Ravetch, J.V., Poplack, D.G., Waldmann, T.A., and Leder, P. Developmental Hierarchy of Immunoglobulin Gene Rearrangement in Human Leukemic Pre-B-Cells. Proc. Nat'l Acad. Sci. U.S.A. 78:7096-7100, 1981.

Larson, S. Radiolabeled Monoclonal Anti-Tumor Antibodies in Diagnosis and Therapy. J. Nucl. Med. 26:538-545, 1985.

Laurence, D.J.R. and Neville, A.M. The Detection and Evaluation of Tumor Metastases. Cancer Metastasis Rev. 2:351-374, 1983.

Lee, W.-H., Murphree, A.L., and Benedict, W.F. Expression and Amplification of the N-myc Gene in Primary Retinoblastoma. Nature 309:458-460, 1984.

Lloyd, K.O. Antigenic Markers for Epithelial Cancer of the Ovary. In Carcinoma of the Ovary, Gustav Fisher Verlag, New York, 1983.

Mach, J.P., Carrel, S., Merenda, C., Sordat, B., and Cerottini, J.C. In Vivo Localization of Radiolabeled Antibodies to Carcinoembryonic Antigen in Human Colon Carcinoma Grafted in Nude Mice. Nature (London) 248:704-706, 1974.

Mahaley, M.S.,Jr. and Day, E.D. Immunological Studies of Human Gliomas. J. Neurosurgery 23:363-370, 1965.

Mitelman, F. Catalog of Chromosome Aberrations in Cancer, Second Edition. Alan R. Liss, N.Y. 1985.

Mitelman, F. and Levan G. Clustering of Aberrations to Specific Chromosomes in Human Neoplasms. IV. A Survey of 1,871 Cases. Hereditas 95:79-139, 1981.

Moldofsky, P.J., Sears, H.F., Mulhearn, C.B. Jr., Hammond, N.D., Powe, J., Gatenby, R.A., Steplewski, Z., and Kaprowski, H. Detection of Metastatic Tumor in Normal-Sized Retroperitoneal Lymph Nodes by Monoclonal-Antibody Imaging. N. Eng. J. Med. 311:106-107, 1984.

Neel, B.G., Jhanwar, S.C., Chaganti, R.S.K., and Hayward, W.S. Two Human c-onc Genes are Located on the Long Arm of Chromosome 8. Proc. Nat'l Acad. Sci. U.S.A. 79:7842-7846, 1982.

Nowell, P.C. Phytohemagglutinin: An Initiator of Mitosis in Cultures of Normal Human Leukocytes. Cancer Res. 20:462-466, 1960.

Nowell, P.C. and Hungerford, D.A. A Minute Chromosome in Human Chronic Granulocytic Leukemia. Science 132:1497, 1960.

Olsson, L. and Kaplin, H. Human-Human Hybridomas Producing Monoclonal Antibodies of Predefined Antigenic Specificity. Proc. Natl. Acad. Sci. U.S.A. 77:5429-5431, 1980.

Osborn, M. and Weber, K. Biology of Disease: Tumor Diagnosis by Intermediate Filament Typing: a Novel Tool for Surgical Pathology. Lab. Invest. 48:372-394, 1983.

Papsidero, L.D., Wojcieszyn, J.W., Horoszewicz, J.S., Leong, S.S., Murphy, G.P., and Chu, T.M. Isolation of Prostatic Acid Phosphatase-Binding Immunoglobin G from Human Sera and its Potential Use as a Tumor Localizing Reagent. Cancer Res. 40:3032-3035, 1980.

Pressman, D. The Zone of Activity of Antibodies as Determined by the Use of Radioactive Tracers. Ann. N.Y. Acad. Sci. 11:203-206, 1949.

Pressman, D. and Keighley, G. The Zone of Activity of Antibodies as Determined by the Use of Radioactive Tracers; The Zone of Activity of Nephrotoxic Antikidney Serum. J. Immunol. 59:141-146, 1948.

Primas, F.J., Wang, R.H., Goldenberg, D.M., and Hansen, H.J. Localization of Human GW-39 Tumors in Hamsters by Radiolabeled Heterospecific Antibody to Carcinoembryonic Antigen. Cancer Res. 33 2977-2982, 1973.

Ramackers, F.C., Haag, D., Jap, P., and Vooijs, P.G. Immunochemical Demonstration of Keratin and Vimentin in Cytologic Aspirates. Acta Cytol. 28:385-392, 1984.

Rowley, J.D. A New Consistent Chromosomal Abnormality in Chronic Myelogenous Leukemia Identified by Quinacrine Fluorescence and Giemsa Banding. Nature 243:290-293, 1973.

Rowley, J.D. Mapping of Human Chromosomal Regions Related to Neoplasia: Evidence from Chromosomes 1 and 17. Proc. Nat'l Acad. Sci. U.S.A. 74:5729-5733, 1977.

Seabright, M. A Rapid Banding Technique for Human Chromosomes. Lancet 2:971972, 1971.

Sheibani, K. and Tubbs, R.R. Enzyme Immunohistochemistry: Technical Aspects. Seminars in Diagnostic Pathology 1:235-250, 1984.

Sparkes, R.S., Murphree, A.L., Lingua, R.W., Sparkes, M.C., Field, L.L., Funderburk, S.J., and Benedict, W.F. Gene for Hereditary Retinoblastoma Assigned to Human Chromosome 13 by Linkage to Esterase D. Science 219:971-973, 1983.

Tsujimoto, Y., Yunis, J., Onorato-Showe, L., Erikson, J., Nowell, P.C., and Croce, C.M. Molecular Cloning of the Chromosomal Breakpoint of B-Cell Lymphomas and Leukemias with the t(11;14) Chromosome Translocation. Science 224:1403-1406, 1984.

Umbach, G. Review of Tumor Markers for Ovarian Cancer. Medical Hypotheses 13:329-339, 1984.

Van Brunt, J. More Than One Way to Zap a Cell. Bio/Technology 3: 187-191, 1985.

Virtanen, I., Partanen, P., Miettinen, M., and Lehto, V.P. Antibodies to Intermediate Filaments in Diagnostic Histopathology. Int. Clin. Prod. Rev. November, 1983.

Wang, H.C. and Federoff, S. Banding in Human Chromosomes Treated with Trypsin. Nature New Biol. 235:52-53, 1972.

Wright, G.L. Jr., Beckett, M.L., Starling, J.J., Schellhammer, P.F., Sieg, S.M., Ladaga, L.E., and Poleskic, S. Immunohistochemical Localization of Prostate Carcinoma - Associated Antigens. Cancer Res. 43:5509-5516, 1983.

Yam, L.T., Winkler C.F., Janckila, A.J., Li, C.Y., and Lam, K.W. Prostatic Cancer Presenting as Metastatic Adenocarcinoma of Undetermined Orgin: Immunodiagnosis by Prostatic Acid Phosphatases. Cancer 51:203-287, 1983.

Yunis, J.J. High Resolution of Human Chromosomes. Science 191:1268-1270, 1976.

Yunis, J.J. The Chromosomal Basis of Human Neoplasia. Science 221:227-240, 1983.

Yunis, J.J. and Ramsey, N. Retinoblastoma and Subband Deletion of Chromosome 13. Amer. J. Dis. Child. 132:161-163, 1978.

P01 CA04486 Pathology of Digestive Tract and Other Mucous Membranes
Zamcheck Boston City Hospital

R01 CA16910 Chromosome Aberration in Myeloproliferative Diseases
Rowley University of Chicago

R01 CA22794 Human Neuroblastoma Antigens
Seeger University of California, LA

R01 CA23945 Assessment of Malignancy in Human Chondrosarcomas
Rosenberg Montefiore Hospital and Medical Center

R01 CA25055 Cytogenetics of Clonal Neoplasias
Hecht Southwest Biomedical Research Institute

R01 CA30627 In Vivo Release of Transformed Cell-Specific Proteins
Webb Ohio State University

R01 CA30687 Progesterone-Specific Protein in Endometrial Secretions
Richardson Massachusetts General Hospital

R01 CA31024 Fine Chromosomal Defects in Leukemia & Myelodysplasia
Yunis University of Minnesota of Minneapolis, St. Paul

R01 CA31218 Thyrotropins from Tumors of Trophoblastic Origin
Amir Beth Israel Hospital

R01 CA33207 Calcitonin in Thyroid Carcinoma
Sorenson Dartmouth College

R01 CA33615 Multiple Forms of HGH: Measurements and Actions
Vander Laan Whittier Institute for Diabetes & Endocrinology

R01 CA33739 Porphyrins in Cancer Treatment: Molecular-Level Studies
Margalit Tel-Aviv University

R01 CA34881 Biochemical and Clinical Application of Acid Phosphatase 5
Lam University of Texas Health Sciences Center

R01 CA35329 Systematic Study of Three Types of Glycosyltransferases
Matta Roswell Park Memorial Institute

R23 CA35602 Secretory Activity of C-Cells in Pathologic Conditions
Halpern Massachusetts General Hospital

R01 CA37200 Metabolism of Carcinoembryonic Antigen
Thomas Mallory Institute of Pathology Foundation

R01 CA37506 GAG as Bladder Cancer Markers in High-Risk Populations
Hurst University of Oklahoma Health Sciences Center

R01 CA38797 Studies on CA Antigen and Related Glycoproteins
Bhavanandan Pennsylvania State University

R01 CA39233 A Study of Cancer Associated Colonic Mucin
Boland University of Michigan

R01 CA39431 Thioesterase II a New Breast Cancer Marker
Smith Children's Hospital Medical Center

R01 CA39641 Serum Tyrosyl Kinases in Human Neoplasia
Clinton Louisiana State University Medical Center

R23 CA40936 Protein Markers of Renal Cell Carcinoma
Tracy University of Vermont

IMMUNODIAGNOSIS

R01 CA18404 Neuroendocrine Differentiation in Human Tumors
Baylin Johns Hopkins University

R01 CA19304 Human Leukemia & Lymphoma Associated Antigens
Seon Roswell Park Memorial Institute

R01 CA19613 Ectopic Hormones in Small Cell Carcinoma of the Lung
North Dartmouth College

R01 CA21399 Binding of Bacteria to Normal & Leukemic Lymphocytes
Teodorescu University of Illinois Medical Center

R01 CA22595 Detection of Medullary Thyroid Cancer in Families
Jackson Henry Ford Hospital

R01 CA25088 Human Ribonucleases and Cancer
Glitz University of California, LA

R01 CA25338 Thyroglobulin Radioimmunoassay in Thyroid Cancer
Charles University of California, Irvine

R23 CA27623 Characterization of Prostate Cell Plasma Membranes
Starling Eastern Virginia Medical School

R01 CA29639 Tumor Imaging with Radiolabelled Monoclonal Antibody
Nelp University of Washington

R01 CA30019 Purification of Tumor Antigens of Defined Specificities
Gupta University of California, L.A.

R01 CA30020 The Cell Surface Phenotype of Malignant Lymphoma
Aisenberg Massachusetts General Hospital

R01 CA31762 Immunologic Diagnosis of Myeloblastic Leukemia
Taub Columbia University School of Medicine

R01 CA32245 Detection & Characterization of Mesenchymal Antigens
Hirshaut Sloan-Kettering Institute for Cancer Research

R01 CA32302 Controlled Trial: CEA Prompted 2nd Look in Bowel Cancer
Slack University of London

R01 CA33239 Tissue Blood Group Antigens in Urothelial Neoplasia
Limas University of Minnesota of Minneapolis - St. Paul

R01 CA33425 Human Myeloma Cell Line
Bernier Dartmouth College

R01 CA33767 Bombesin-Like Peptides in Oat Cell Carcinoma
Moody George Washington University

R01 CA34039 Carbohydrate Determinants as Human Tumor Markers
Lloyd Sloan-Kettering Institute for Cancer Research

R01 CA34187 Monoclonal Antibodies in Diagnosis & Prognosis of Cancer
Chee Scott Laboratories, Inc.

R01 CA34635 Preneoplastic Markers Detected by Monoclonal Antibodies
Dunsford University of Texas Health Science Center Houston

R01 CA34782 Immunological Detection of Pyrimidine Dimers in Situ
Ley Lovelace Medical Center

R01 CA35227 Human and Murine Hybridoma Antibodies in Acute Leukemias
Olsson University of Copenhagen

R01 CA35354 Monoclonal Antibodies to Human Sarcoma Membrane Antigens
Brown University of Illinois at Chicago

R01 CA35460 Monoclonal Anti-Ebna Antibodies
Volsky University of Nebraska Medical Center

R01 CA36310 Cell Lines & Methods for Human Hybridomas
Heitzmann Salk Institute for Biological Studies

R01 CA36320 New Approach to Produce Human Monoclonal Antibodies
Volsky University of Nebraska Medical Center

R01 CA36422 Heteromyelomas for Human Monoclonal Antibody Production
Teng Stanford University

R01 CA36450 Isolation of a Hodgkin-Related Antibody
Taylor University of Southern California

R01 CA36553 Radiolabeled Antibody Localization of B-Cell Lymphoma
Buchsbaum University of Minnesota of Minneapolis - St. Paul

R01 CA36903 Radioimmunodetection of Pancreatic Tumors
Cheng University of Iowa

R01 CA36934 Immunocytochemical Studies of Prostatic Acid Phosphatase
Lam University of Texas Health Sciences Center

R01 CA37407 AFP/HCG Radioimmunodetection in Testicular Cancer
Goldenberg University of Medicine & Dentistry of NJ

R01 CA37408 Clinical CEA-Tumor Radioimmunodetection
Goldenberg University of Medicine & Dentistry of NJ

R01 CA37409 CSAP Radioimmunodetection of Colorectal Cancer
Goldenberg University of Medicine & Dentistry of NJ

R01 CA37411 Immunological Heterogeneity of CEA
Primus University of Medicine & Dentistry of NJ

R01 CA37412 Radiological Localization of Human Tumors
Goldenberg University of Medicine & Dentistry of NJ

R01 CA38160 Sequence Specific Hybridomas to Growth Factors
Niman Scripps Clinic and Research Foundation

R01 CA38355 Viral Proteins: Possible Systemic Signals for Tumors
Ritzi Texas Tech University

R01 CA38879 Immunodiagnostic Approaches to Human Breast Cancer
Kufe Dana-Farber Cancer Institute

R01 CA38909 Circulating Malignant Cells in Non-Hodgkin's Lymphoma
Weinberg Brigham & Women's Hospital

R23 CA39237 Bombesin-like Peptides: Structure and Physiology
Spindel Joslin Diabetes Center

R35 CA39841 Radioimmunodetection of Cancer
Goldenberg Center for Molecular Medicine and Immunology

R01 CA39932 Circulating Tumor Components
Ceriani John Muir Memorial Hospital

R13 CA40005 Labelled and Unlabelled Antibody in Cancer Diagnosis and Therapy
Order The Johns Hopkins University

R01 CA40608 Development and Characterization of Myeloma Cell Lines
Epstein University of Southern CA

R01 CA41166 Specificity of Antitransforming Gene Product Antibody
Sklar University of Michigan at Ann Arbor

R01 CA13271 Automated Cancer Cell Diagnosis by the TICAS Method
Wied University of Chicago

R01 CA23393 Flow Analysis of Human Malignant Lymphoid Cells
Braylan University of Florida

R01 CA24466 Ultrafast Scanner Microscope in Laboratory Automation
Shack University of Arizona

R01 CA27313 Diagnosis of Sputum Atypias by Cell Image Analysis
Greenberg Baylor College of Medicine

R01 CA28704 Chromatin Probes for Distinguishing Malignant Cells
Darzynkiewicz Sloan-Kettering Institute for Cancer Research

R01 CA28706 Cell Positioning System: Development and Use in Cancer
Tyrer Cancer Research Center

R01 CA28770 Biophysical Probes for Automated Cytology
Atkinson University of Pennsylvania

R01 CA28771 Cytology Automation
Barlogie University of Texas System Cancer Center

R01 CA28921 Merocyanine Dyes as Leukemia-Specific Probes
Schlegel Pennsylvania State University Park

R01 CA30582 Multidimensional Slit-Scan Proscreening System
Wheeless University of Rochester

R01 CA31718 Automated Cytology Prototype Development
Castleman California Institute of Technology

R01 CA32314 Fluid Cell Sorter
Wheeless University of Rochester

R01 CA32345 Computer Image Analysis of Cells in Urothelial Cancer
Koss Montefiore Medical Center

R01 CA33148 Multidimensional Slit-Scan Detection of Bladder Cancer
Wheeless University of Rochester

R01 CA34870 Nuclear DNA and Morphometric Studies of Gynecologic Cancer
Fu University of California, LA

R01 CA35898 Quantitative Probes in Cancer Prevention & Diagnosis
Hemstreet University of Oklahoma Health Sciences Center

R01 CA37349 Improved Cancer Diagnosis by Morphometric Analysis
Rosenthal University of California, LA

R01 CA37352 Tumor Diagnosis by Rapid DNA Ploidy Pattern Analysis
Bibbo University of Chicago

R01 CA37368 Cell Morphology in Follicular & Diffuse Lymphomas
Preston Carnegie-Mellon University

P01 CA38548 Fast Digital Microscope Designs for Tumor Diagnosis
Bartels University of Arizona

R01 CA39022 Flow Cytometric Analysis of DNA in Human Lymphoma Cells
Braylan University of Florida

R13 CA39341 Advance in Morphometry and Ploidy Determination
Bahr Armed Forces Institute of Pathology

R01 CA39569 Biology of Calla + Cells in Lymphobastic Leukemia
Ryan University of Rochester

PATHOLOGY

R13 CA05096 Program of the International Union Against Cancer
Veronesi International Union Against Cancer

R01 CA14264 Pathology of Cell Differentiation in Leukemia
Bainton University of California, San Francisco

R01 CA22101 Study of Head and Neck Cancer by Serial Section
Kirchner Yale University

R01 CA25582 Diagnostic Imagining Fluorescence Bronchoscopy
Balchum University of Southern California

R01 CA26422 Clinico-Biologic Correlation in Lymphoma and Leukemia
Rappaport City of Hope National Medical Center

R01 CA33618 Preclinical Training in Endoscopic Programs
Rayl VA Medical Center Lake City, Florida

R01 CA33717 Bronchioloalveolar Carcinoma: Diagnosis and Pathobiology
Singh University of Pittsburgh

R01 CA36245 Intermediate Filament Proteins as Tumor Markers
Trojanowski University of Pennsylvania

R01 CA36250 Cytoskeletal Hybridoma Antibodies as Diagnostic Reagents
Gown University of Washington

R01 CA36902 Macromolecular Transport in Neoplastic Capillary Beds
Jain Carnegie-Mellon University

R01 CA37083 Monoclonals for Immunodiagnosis of Processed Tissues
Rouse Stanford University

R01 CA37194 Monoclonal Antibodies in Classification of Tumors
Battifora City of Hope National Medical Center

R01 CA37944 Immunohistochemical Classification of Human Breast Tumors
Raam Tufts University

R01 CA39353 Endocrine-Paracrine (Apud) Cells and Prostate Pathology
Di Sant'Agnese University of Rochester

GENETICS

R01 CA32066 Genetic Linkage in Multiple Endocrine Neoplasia, Type II
Genel Yale University, New Haven

R01 CA33314 Fine Chromosomal Defects in Non-Hodgkin's Lymphoma
Yunis University of Minnesota

R01 CA35040 Early Detection of Medullary Thyroid Carcinoma
Samaan University of Texas System Cancer Center

R01 CA38583-01 Recombinant DNA Technology to Pediatric Cancer
Cavenne University of Cincinnati

R01 CA35966 MHC and Cancer Susceptibility Genes in Man
Gatti University of California, LA

R01 CA37866 Analysis of Human Oncogene Polymorphisms
Krontiris Tufts University School of Medicine

R01 CA38569 Diagnosis of Leukemia (CML) Oncogene (C-ABL) Expression
Gale University of California, LA

R01 CA38579 Mutant Ras Oncogenes in Human Tumors
Perucho State University New York Stony Brook

R01 CA38621 Genetic Studies of Human B Cell Cancer
Sklar Stanford University

R01 CA39771 Molecular Genetic Analysis of Human Neuroblastoma
Brodeur Washington University

R01 CA39926 Cytogenetic and Molecular Studies of Human Chromosome 22
Emanuel Children's Hospital of Philadelphia

R13 CA40716 Workshop on Chromosomes in Solid Tumors
Trent University of Arizona

R01 CA40728 c-abl Oncogene Expression in CML
Collins Fred Hutchinson Cancer Research Center

R01 CA40957 Molecular Diagnosis of Chronic Myelogenous Leukemia
Witte University of California, L.A.

SBIR

R44 CA36657 Cervical Cancer Detection and Screening (Phase II)
Bacus Cell Analysis Systems, Inc.

R43 CA36660 Human Liver Cancer Serum Marker
Hillman Antibodies, Inc.

R43 CA38501 Production of Monoclonal Antibodies to Antigen
Jordan JCL Clinical Research Corporation

R43 CA39867 Immunoassay for Squamous Cell Carcinoma Serum Antigens
Jones Carcinex, Inc.

R43 CA39876 DNA Probe for Detection of Viral Nucleic Acid
Manak Biotech Research Laboratories, Inc.

R43 CA39880 Diagnosis of Viral Genes in Whole Blood
Eincka HEM Engineering Company

R43 CA39885 Non-Enzymatic Immunohistochemistry
Shochat Immunomedics, Inc.

R43 CA39937 High Resolution Separation System for Small Peptides
Iida Peptide Analysis Laboratory

R43 CA39941 Research on Micro-GCMS for Biomedical Applications
Drew Viking Instruments Corporation

R43 CA40792 Monoclonal Antibody Based Test for Occult Blood
Mueller Summa Medical Corporation

R43 CA40800 Glycolipid Antigens in the Diagnosis of Adenocarcinoma
Singhal Imre Corporation

R43 CA40860 Amylase Isozyme Determination with Monoclonal Antibodies
Woodward Unogen Inc.

R43 CA40945 Early Detection of Ovarian Carcinoma: Phase I
Zurawski Centocor Inc.

R43 CA40939 Antigens Associated with Aids-Kaposi Sarcoma
Snyder Imre Corporation

CONTRACT RESEARCH SUMMARY

Title: Human Tumor Cell Line Bank for Diagnostic Studies

Principal Investigator:	Dr. Robert J. Hay
Performing Organization:	American Type Culture Collection
City and State:	Rockville, MD

Contract Number: NO1-CB-14351
Starting Date: 9/29/81 Expiration Date: 9/28/86

Goal: The objectives of the program are to acquire, characterize, catalog, store and distribute a variety of cell lines having special utility for research in tumor diagnosis. Well characterized lines from solid tumors as well as from normal tissues will be included. Information concerning properties and utility of these lines will be provided to all interested investigators.

Approach: Cell lines selected in consultation with the Government Project Officer (GPO) and advisors will be expanded from token holdings or new submissions to produce seed and distribution stocks. These will be characterized using published ATCC procedures. Initially, standard tests for the absence of microbial contamination will be applied and species verification will be accomplished by assay for the isoenzymes of glucose-6-phosphate dehydrogenase, lactic dehydrogenase and nucleoside phosphorylase. Distribution will begin following satisfactory completion of these tests. Lines in the existing bank are being characterized further with regard to isoenzyme profiles, karyology, surface antigens, etc. as time and funds permit.

Progress: The lines selected from the former cell bank by the advisory committee were recharacterized and catalogued for distribution. In addition, 15 human breast cancer lines were transferred to the ATCC from the EG & G Mason Institute and token stocks of a variety of other human cell lines (965) were transferred from the Naval Biosciences Laboratory (NBL). Fourteen of the former 127 and of the latter were initially selected from the NBL lines for examination and possible addition to the bank. Twenty of the 127 NBL lines and the 14 EG & G Mason lines were characterized and found suitable for inclusion in the Bank. Many of the NBL lines were eliminated because they were stromal in nature. In general, fibroblast-like lines have not been included unless a tumor line from the same patient is also available. To date, the Human Tumor Cell Line Bank consists of 126 lines. These are shipped for a fee upon request along with directions on reconstitution and culture. An average of 166 cell lines have been shipped per month during the past 12 month interim.

Project Officer: Roger L. Aamodt, Ph.D.
Program: Diagnosis
FY 85 Funds: $162,074

B/A

CONTRACT RESEARCH SUMMARY

Title: Biological Markers in Breast Cancer: Patient Resource

Principal Investigator: Dr. Theodore Maycroft
Performing Organization: Butterworth Hospital
City and State: Grand Rapids, MI

Contract Number: NO1-CB-23927
Starting Date: 9/15/82 Expiration Date: 9/14/86

Goal: To develop a specimen resource for blood from breast cancer patients and benign disease patients to be used in a search for and verification of new breast cancer markers.

Approach: Thirty milliliters of blood are collected prior to surgery from breast disease patients scheduled for biopsy and/or primary surgery for breast lesions. Another specimen when feasible from the same patient is collected 5-10 weeks postmastectomy. Annual collections are made on patients with malignant diagnoses. Patients with benign diagnoses are asked to complete annual questionnaires for two years after biopsy. Serum specimens are stored at $-70^{o}C$, then shipped to an NCI designated blood bank facility. Appropriate clinical data is sent to a central data center.

Progress: Surgeons who perform 95% of all breast biopsies in any of the three participating institutions have made formal agreements to allow their patients to directly enter the study. Since the inception of the program, 4,457 patients have become participants in the project; 1016 of these patients have been found to have malignant breast disease. Approximately 67,000 vials containing serum specimens have been shipped to the central storage facility at Mayo Clinic. 1487 collections have been made on the annual anniversary of malignant disease patients and 3,943 follow-up questionnaires have been completed on benign disease patients. This information has been forwarded to the central data center.

Project Officers: Roger L. Aamodt, Ph.D. and Judith M. Whalen, M.P.A.
Program: Diagnosis
FY 85 Funds: $55,072

A

CONTRACT RESEARCH SUMMARY

Title: Biological Markers in Breast Cancer: Patient Resource

Principal Investigator: Dr. Harold D. Lankford
Performing Organization: Cancer Research Center
City and State: Columbia, MO

Contract Number: NO1-23925
Starting Date: 9/01/82 Expiration Date: 8/31/86

Goal: To serve as a specimen resource for serum from breast cancer patients and controls to be used in a search for and verification of new breast cancer markers.

Approach: Since late 1977, blood samples have been drawn from volunteer Breast Cancer Demonstration Detection Project and Women's Cancer Control participants and in two local hospitals from patients scheduled for breast surgery. In addition, post-mastectomy (30 to 100 days) and annual samples are drawn from women with a diagnosis of breast cancer. With appropriate consent, 30 ml of blood is collected and processed into 10-13 one ml aliquots of serum. The serum is stored at -70°C and frozen samples shipped to the Mayo Clinic for storage and dissemination. Associated clinical data is sent to and retained by the central data center, Information Management Services (IMS). Clinical histories are updated at one year for patients with benign biopsies and annually for two years from normal participants.

Progress: By March 31, 1985, 13,467 samples of blood had been drawn on 7634 different participants. This included 6733 control women, 350 pre-op benign, 231 pre-op malignant and 478 other malignant. On April 30, 1984, Mayo Clinic reported that they have in storage 144,564 vials submitted from Columbia. In addition, clinical update histories have been submitted to IMS on 6845 participants. Because of special efforts on the part of the serum markers personnel and a cooperative effort with the Women's Cancer Control Program, we have only had to designate 16 participants as lost to followup.

Project Officers: Roger L. Aamodt, Ph.D. and Judith M. Whalen, M.P.A.
Program: Diagnosis
FY 85 Funds: $62,004

A

CONTRACT RESEARCH SUMMARY

Title: Biomedical Computing Support of Breast Cancer Markers Program

Principal Investigator:	Ms. Marlene Dunsmore
Performing Organization:	Information Management Services, Inc.
City and State:	Bethesda, MD
Contract Number:	NO1-CB-14339
Starting Date:	3/31/81
Expiration Date:	6/14/85

Goal: To increase the usefulness of the data generated in projects related to the diagnosis of human breast cancer.

Approach: A central file was developed by the contractor for the breast tumor biomarkers program. This file allows preparation of various serum panels for testing new biological markers for breast cancer, setting up studies on multiple markers involving multiple institutions, and comparisons of the results from various studies and provides a database from which material can be quickly and conveniently retrieved. This data file is also intended for testing new ideas, identifying groups of subjects suitable for more detailed study and for preparing reports to the medical community and the general public.

Progress: Biomedical computing support for the Breast Cancer Biological Markers Program has continued in an exemplary manner. To date more than 22,000 forms reporting background and clinical data have been received and added to the file. The current work scope is limited primarily to Breast Cancer Serum Bank activities, but a limited number of data analyses for the Diagnosis Serum Bank are also included. The processing of various forms continues to be the main workload. Data from two collection centers is checked for consistency verified and stored. Clinical data for the Breast Cancer Bank is maintained and coded panel composition determined by the Contractor. Analysis of results using sophisticated statisitical techniques is being accomplished for all Breast Cancer Serum Bank users and selected Diagnosis Serum Bank users.

Project Officers: Roger L. Aamodt, Ph.D. and Judith M. Whalen, M.P.A.
Program: Diagnosis
FY 85 Funds: 0

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CONTRACT RESEARCH SUMMARY

Title: NCI Sera Bank Facility: Biological Markers in Breast Cancer

Principal Investigator: Dr. Vay Liang Go
Performing Organization: Mayo Foundation
City and State: Rochester, MN

Contract Number: NO1-CB-33931
Starting Date: 2/01/83 **Expiration Date:** 08/31/85

Goal: To establish and maintain a storage facility for serum specimens to be used in a program designed to search for biological markers in breast cancer.

Approach: Serum specimens are being secured from breast cancer patients, benign disease patients, normal controls, and a screening population under the separate collection contracts. The material is being shipped to Mayo and processed, recorded and stored in -70°C freezers under easily retrievable conditions. Clinical data are available in a central data center. The sera will be used in the search for and verification of new breast cancer markers.

Progress: Storage and inventory methods have been developed. A special vial has been designated and is being supplied to the collection areas. An operational shipping schedule has been established on a regular basis. Samples have been catalogued and systematically stored in 36 freezers. Inventory collected up to February 20, 1985 is listed below:

Collection Centers	No. Patients	No. Vials	No. Shipments
A. Wilmington, Delaware	595	6,131	50
B. Grand Rapids, Michigan	6,745	70,201	159
C. Columbia, Missouri	13,464	144,428	121
(Total number of patients includes annual drawings)	20,804	220,760	330

Since June 19, 1979, 25 coded serum panels have been shipped to individual investigators for evaluation of new breast cancer markers.

Project Officers: Roger L. Aamodt, Ph.D. and Judith M. Whalen, M.P.A.
Program: Diagnosis
FY 85 Funds: 0

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CONTRACT RESEARCH SUMMARY

Title: Maintenance of the NCI Serum Diagnostic Bank

Prinicipal Investigator: Dr. Vay Liang W. Go
Performing Organization: Mayo Foundation
City and State: Rochester, MN

Contract Number: N01-CB-84258
Starting Date: 9/30/78 Expiration Date: 8/31/85

Goal: To establish and maintain a bank of frozen sera from patients with cancer, patients with benign diseases and from normal individuals, for the evaluation of immunodiagnostic and biochemical tests of potential clinical usefulness in the diagnosis of cancer.

Approach: Collect and make serum samples available for validation of biochemical and immunodiagnostic tests for cancer. Serve as a central facility for storage of serum and plasma specimens collected by other contractors in the Diagnosis Program.

Progress: A bank of sera from patients with histologically diagnosed malignancies, benign diseases and healthy individuals is established and maintained. A computerized clinical data and inventory system is also in operation. Sera are stored at -70°C with adequate continuous temperature monitoring and quality control. The sera are made available as coded panels by the Project Director, in response to requests from investigators, for evaluation of immunodiagnostic, hormonal and enzymatic tests for cancer. The coded serum panels are adequate to determine the sensitivity and specificity of specific tumor markers and their comparative values with other tumor markers. The current inventory also includes blood collected from the University of Minnesota and the Philadelphia Geriatric Center, for long term storage under former contracts which is stored in 51 freezers at -70°C.

During the past year, April 1984 through March 1985, 24 panels were shipped to U.S. Investigators. The collection stood at a level of 102,489 specimens as of March 15, 1985. There are, in addition, a total of 177,487 vials from other investigators in the collection, 119,007 from University of Minnesota, 41,975 from Philadelphia Geriatrics 13,917 from Memorial Sloan-Kettering and 2,588 from Emory University.

Project Officers: Roger L. Aamodt, Ph.D. and Judith M. Whalen, M.P.A.
Program: Diagnosis
FY 85 Funds: $149,716

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CONTRACT RESEARCH SUMMARY

Title: Screening Technique for Blood in Stool to Detect Early Cancer of Bowel

Principal Investigator: Dr. Victor A. Gilbertsen
Performing Organization: University of Minnesota Health Sciences Center
City and State: Minneapolis, MN

Contract Number: NO1-CB-53862
Starting Date: 6/30/75 Expiration Date: 12/31/88

Goal: To demonstrate significant reduction in mortality from colorectal cancer between the screened and the control groups. The test groups will be screened employing the Hemoccult (R) form of the guaiac test for occult blood in the stool in combination with a diagnostic protocol to locate the source of bleeding if the test is positive.

Approach: Forty-five thousand participants between 50 and 80 years of age with no prior history of colorectal cancer and residing in the state of Minnesota, were randomized into three groups (two experimental, one control) by age, sex and geographic region of the state. Guaiac slides were completed and returned to the University by mail to be developed. Test groups submitted slides annually or biennially; the control group did not submit slides. Participants submitting slides positive for blood were evaluated using the diagnostic protocol at the University of Minnesota hospitals and clinics; this included a complete history and physical examination, upper G.I. series x-ray (and gastroscopy if indicated), proctoscopy and colonoscopy.

Progress: The initial screening phase of the study was completed in December, 1982. Follow-up procedures to determine the vital status and monitor the incidence of disease among the participants are continuing. Contact has been maintained with over 95% of the participants. The Policy and Data Monitoring Group, established in 1984 to assess the data, recommended that screening be resumed; this appears to be necessary in order to increase the statistical power of the study. Resumption of screening will begin in the Spring of 1985 and continue for five years. During this period, follow-up will also continue and all deaths will be recorded. All cancer deaths receive particular attention for colorectal involvement; all deaths involving colorectal malignancy are carefully evaluated by the Death Review Committee to determine whether the individual died from or with colorectal cancer.

Project Officers: Ihor Masnyk, Ph.D., Sheila E. Taube, Ph.D, & Philip Prorok, Ph.D.
Program: Diagnosis
FY 85 Funds: $1,334,428 A

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